

# **EXHIBIT C10**

**IN THE UNITED STATES DISTRICT COURT  
FOR THE DISTRICT OF NEW JERSEY**

**IN RE: JOHNSON & JOHNSON TALCUM  
POWDER PRODUCTS MARKETING, SALES  
PRACTICES AND PRODUCTS LIABILITY  
LITIGATION**

**MDL NO. 16-2738 (FLW) (LHG)**

***THIS DOCUMENT RELATES TO ALL CASES***

**EXPERT REPORT OF BENJAMIN G. NEEL, MD, PHD  
FOR GENERAL CAUSATION *DAUBERT* HEARING**

Date: February 25, 2019



Benjamin G. Neel, M.D., Ph.D.

## **I. BACKGROUND AND QUALIFICATIONS**

I am the Laura and Isaac Perlmutter Director and Professor of Medicine (with tenure) at NYU School of Medicine. In that capacity, I am responsible for all cancer care and research across NYU Langone Health.

In my role at NYU, I oversee my own 13-person research laboratory, which has been continuously funded by NCI/NIH since 1988. My major expertise is in the area of cancer cell signaling, most notably involving protein-tyrosine phosphatases (PTPs). I am generally recognized as a co-founder of the PTP field, and have authored or co-authored multiple major reviews and co-edited a book in this area.

I received my Ph.D. in Viral Oncology at The Rockefeller University in 1982 in the laboratory of Lasker Awardee Hidesaburo Hanafusa, Ph.D., working directly under William S. Hayward, Ph.D. My thesis work established that slowly transforming RNA tumor viruses caused cancer by inserting themselves next to, and activating, the cellular proto-oncogene *c-Myc*. This finding served as the paradigm for oncogenesis by all such viruses and anticipated the subsequent discovery that many chromosomal translocations (rearrangements) cause cancer in humans by a similar “promoter/enhancer” mechanism. Dr. Hayward was the co-recipient of the Bristol-Myers Squibb award for this discovery.

I received my M.D. from Cornell University Medical School (now Weill-Cornell) in 1983, and completed medical internship and residency training at the former Beth Israel Hospital (now Beth Israel Deaconess Medical Center (BIDMC)) from 1983-85. I am a Diplomate of the American Board of Internal Medicine (board-certification). From 1985-1988, I pursued post-doctoral studies as a Leukemia Society Special Fellow with Lasker Awardee Raymond L. Erikson, Ph.D., in the Department of Cell and Developmental Biology at Harvard University.

In 1988, I was appointed Assistant Professor of Medicine at Harvard Medical School (HMS), and started my own research laboratory at Beth Israel Hospital. I rose through the ranks at HMS, becoming Professor of Medicine in 1999, and also serving as Director of the Cancer Biology Program, from 1994, and Deputy Director for Basic Research, Hematology-Oncology at BIDMC, beginning in 2003. In 2006, I was appointed to the William B. Castle Chair of Medicine at HMS. Under my leadership, Hematology-Oncology rose from the least-funded to the top-funded (in NIH/NCI grants) division in the Department of Medicine at BIDMC. I also recruited three new junior faculty, two of whom are now Professors of Medicine at HMS.

In 2007, I became Director of Research at Princess Margaret Cancer Center (PMCC) in Toronto, Canada, and Senior Scientist and Canada Research Chair, Tier 1, in the Departments of Medical Biophysics and Biochemistry at the University of Toronto. In that capacity, I recruited more than 20 new investigators, and established new programs in Clinical Cancer Genomics, Epigenetics, Computational Biology and Tumor Immunology/Immune Therapy. During my tenure, PMCC ranked 3<sup>rd</sup> or 4<sup>th</sup> year over year in percentage of high-impact publications among North American cancer centers, and grant and philanthropic funding each increased by more than 50% on a yearly basis.

During my time at PMCC, my group also developed a significant interest in ovarian cancer pathogenesis and functional genomics. I have authored several papers in this area, chaired the Current Topics in Ovarian Cancer session at the American Association for Cancer Research (AACR) annual meeting in 2014 and co-chaired the AACR Ovarian Cancer Conference in 2015. Overall, I have published 234 peer-reviewed primary manuscripts and 33 invited reviews, which together have attracted more than 45,000 citations. I have an h-index of 107 and an i10 of 236.

Since assuming my position at NYU Langone in January 2015, I have recruited 38 new investigators from external institutions, restructured our entire leadership team and successfully renewed our NCI Cancer Center Support Grant with a score of “Outstanding” and “Comprehensive Cancer Center” designation.

In addition to my institutional experiences, I have had a number of national and international leadership roles. I have chaired or co-chaired numerous important scientific meetings, including Gordon Conferences, FASEB meetings, and Cold Spring Harbor (CSH) meetings, all of which are major meetings in the fields of cancer biology and signal transduction. I am currently co-chair of the CSH Meeting on Cancer, through 2021. Chairing/co-chairing such conferences is generally recognized as indicative of world leadership in the field. In 2012, I was the Program Chair for the AACR annual meeting, which attracts nearly 20,000 cancer researchers from around the world. As Program Chair, I was responsible for selecting leaders for all of the sessions, and ultimately responsible for the entire meeting program and its execution. From 2012-2015, I served as an elected member of the AACR Board of Directors. I have been a member on several AACR award selection committees, and just completed service as Chair of the committee to select the AACR Lifetime Achievement Award. I also have served as a full member on two NIH study sections, and as an external reviewer of the intramural program at NCI-Frederick, program project grants, and Cancer Center grants. I am a member of the external advisory boards of 3 NCI-designated Comprehensive Cancer Centers (Columbia, Northwestern, Rutgers-CINJ). I also was an Editor of the journal *Molecular and Cellular Biology* from 1991 to 2000, and currently serve on the editorial boards of multiple major cancer and cellular/molecular biology journals, including the two most highly rated specialized journals for Cancer Biology, *Cancer Cell* and *Cancer Discovery*.

I have also been fortunate to receive several awards in recognition of my research. I was the first recipient of the Gertrude Elion Award from the AACR. I have been elected to the American Association of Physicians, received the Premier of Ontario’s Summit Award (the highest scientific award in Ontario), and held an NIH MERIT award from 2003-2013.

Overall, my own research and multiple leadership experiences have given me broad expertise in cancer biology and medicine, as well as detailed, specific expertise in signal transduction and ovarian cancer pathobiology.

A complete curriculum vitae is attached as an appendix to this report.

I am being compensated at a rate of \$750 per hour for my expert work in this litigation. All of the opinions in this report are stated to a reasonable degree of scientific certainty.

## II. WHAT IS CANCER?

**A brief overview of normal cellular regulation:** Our cells are complex machines, and thus are subject to multiple – and intricate – levels of regulation. The cellular “control center” is the nucleus, which houses 46 chromosomes (23 pairs), composed of “chromatin.” Chromatin comprises DNA wrapped around specific proteins, called histones. “Genes” are units of DNA of variable length that encode the instructions for making proteins, the ultimate workhorses of cells. These instructions are transmitted from the nucleus by messenger RNA (mRNA) to protein synthesis machines, called ribosomes, in the cytosol. The genetic content of an organism is termed its “genome,” and to maintain genomic integrity, when a cell divides, it must replicate its DNA perfectly and reassemble it properly into chromosomes.

Although all cells contain the same genes, different types of cells express different mRNAs, and consequently, distinct proteins. For example, blood cells, skin cells and heart cells express different mRNAs and proteins. Such “differential gene expression” is achieved in multiple ways. Much of the genome comprises DNA (“regulatory regions”) that binds proteins called “transcription factors,” which instruct genes to turn on or turn off. Transcription factors bind specific sequences in the DNA, known as “enhancers” and “promoters,” respectively. Another, more recently described level of gene regulation, often termed “epigenetic,” is mediated at the level of histones or DNA. Histones undergo chemical modifications, such as acetylation, methylation, and phosphorylation, and/or have other proteins (ubiquitin, SUMO) attached to, or removed from, them. This “histone code” regulates the accessibility of different parts of the DNA to transcription factors. Large regions of the genome can be “looped” together to render them susceptible to the same histone modifications, and thereby control blocks of genes together. Looping is mediated by the binding of two proteins, called CTCF and cohesin, which also bind to specific regions (CTCF/cohesin binding sites). Looping and histone movements require “chromatin remodeling,” carried out by so-called “SWI/SNF chromatin remodeling complexes.” Long non-coding RNAs (lncRNAs) also may play important roles in controlling opening and closing of specific regions of chromatin.

These multiple levels of control leave some regions of the genome “open,” and others closed or “compacted.” For a gene to be expressed, it must lie in open chromatin, and its key transcription factors must be expressed and bound to its enhancer/promoter regions. Genes that lie in closed or compacted chromatin can only be expressed if the chromatin is opened by altered epigenetic regulation. DNA, which consists of adenines, guanines, thymine and cytosine residues, can be methylated on specific cytosines. DNA methylation also helps control its packaging into open or closed chromatin, and thereby its access to transcription factors. In general, high levels of methylation (hypermethylation) are associated with closed, inactive chromatin, whereas hypomethylation correlates with open, active gene regions.

Gene expression is also regulated by RNA splicing and microRNAs (miRNAs). Nearly all protein-coding genes are divided into “exons” and “introns.” When a gene is expressed, all of its exons and introns are made into an initial “pre-mRNA,” which is then “spliced” by a multi-protein complex called the “spliceosome.” Splicing stitches exons together, while removing introns. Although most exons (“coding exons”) contain the coding information for proteins, others are “non-coding.” Some non-coding exons bind miRNAs, which inhibit translation of that mRNA by the ribosome, and ultimately cause the mRNA to be degraded. Some genes undergo

“alternative splicing,” whereby specific exons are shuffled in or out in different physiological states or cell contexts. These “alternative splice products” can result in the expression of different proteins from the same gene. Thus, while there are only about 20,000 human genes, these likely encode around 60-80,000 human proteins. Alternative splicing also can leave a miRNA-binding exon in or out of an mRNA, thereby affecting the level of its cognate protein.

Once synthesized, proteins perform all major functions in cells. These include the generation and utilization of energy (“metabolism”), specialized cell functions such as cell movement, antibody production, defense against parasites and other microorganisms, digestion, pumping of blood and food, and reproduction, among others. Specific proteins also enable cells to respond correctly to signals in the external environment. For example, cells receive specific signals known as “growth factors and cytokines,” to begin the process of cell growth and division. They also receive other “growth inhibitory” signals. These analog signals are integrated, via a process termed “signal transduction,” into digital cellular decisions: should the cell divide, move, contract, etc.? Most of these signals are transmitted from specific proteins on the cell membrane termed “receptors” through downstream signaling molecules, to the cell nucleus. Ultimately, signal transduction results in modifications of transcription factors or epigenetic regulators, and changes in gene expression.

Hence, while cellular information flow follows the “Central Dogma” of molecular biology, DNA->RNA->protein, there are many devils in the dogma’s details. For a given protein to be expressed, its gene must reside within open chromatin, and transcription factors that activate its cognate gene must be present and active. The level of that protein is determined by how strongly the particular transcription factor engages the mRNA synthesis machinery, and whether or not miRNAs that control its mRNA are present. There also are additional levels of control of protein synthesis and degradation (“translational” and “post-translational” control, respectively). Proteins, in turn, perform all of the key functions of the cell, including the transmission of signals back to the cellular control center in the nucleus. Remarkably, these processes usually function seamlessly and continuously throughout human life. When they malfunction, however, disease, including cancer, ensues.

**Cancer is a disease of the genome:** Many diseases result from external pathogens (e.g., bacteria, viruses, parasites) that disrupt normal body functions. Cancer, however, is a disease of the genome, caused by “mutations” that affect the intricate control mechanisms described above. Mutations are structural changes in DNA that occur in multiple varieties. “Point mutations” affect single DNA residues, and depending upon their precise location, can have distinct effects. If they affect coding regions of genes, point mutations can increase (“gain-of-function”) or decrease (“loss-of-function”) a protein’s normal activity. Alternatively, point mutations can affect key regulatory regions. For example, mutations that alter CTCF binding sites have been reported; these can lead to altered chromatin structure and aberrant gene expression, as can mutations that affect chromatin remodeling complexes and mutations in CTCF itself. “Structural variants” also contribute to cancer. Chromosomes can break and rejoin incorrectly, resulting in part of one chromosome becoming attached to another, an aberration known as a “translocation.” Some translocations place a gene under the regulatory control of another gene, resulting in inappropriate expression. Others result in “fusion proteins,” in which a piece of one protein is grafted onto another. Fusion proteins typically drive a highly regulated protein into a

constitutively “on” state. Other times, chromosomes –or regions within chromosomes – undergo “amplification” or “deletion.” Amplifications result in an increase in the “copy number” of a specific gene or genes – and thus are gain-of-function mutations. Deletions result in decrease or absence of a specific gene product. Collectively, deletions and amplifications are termed “copy number abnormalities” (CNAs).

Cancer-causing mutations (point mutations, translocations, CNAs) affect specific genes, known as “oncogenes” and “tumor-suppressor” genes. Oncogenes undergo gain-of-function mutations, and encode proteins that tell cells to grow, divide, send out signals to promote new blood formation (“angiogenesis”), and/or escape the immune system. Some oncogenes inhibit a process called “programmed cell death,” which directs cells to commit suicide if they have suffered too much damage. Representative oncogenes include the BCR/ABL fusion protein, the product of the so-called “Philadelphia chromosome” in chronic myelogenous leukemia, which encodes a constitutively active “kinase” and is the target of the drugs Imatinib and Dasatinib, and HER2, which is amplified in ~20% of breast cancer cases (and at a lower rate in some other cancers) and is the target of the drug Herceptin. Tumor suppressor genes undergo loss-of-function mutations, and come in two general categories. Some, such as the so-called “retinoblastoma gene product” (RB), and the *PTEN* gene product, encode proteins that tell cells to stop growing. Others direct DNA repair; these are sometimes termed “caretaker genes.” For example, *BRCA1* and *BRCA2* are tumor suppressor genes whose products control a specific type of DNA repair called “homologous recombination.” Other tumor suppressor genes control “mismatch repair.” The *TP53* tumor suppressor gene is one of the most frequently altered genes in human cancer, and is mutated in virtually all high grade serous ovarian carcinomas. The *TP53* gene product (TP53) tells cells to stop growing, activates the DNA repair machinery, and directs cell death if the DNA damage is not repaired. Because of its multiple, critical functions in maintaining genome integrity, TP53 has been termed the “guardian of the genome” [1-4].

Large-scale sequencing efforts have identified nearly 600 genes whose mutation clearly contributes to human cancer, and many others that might contribute (<https://cancer.sanger.ac.uk/cosmic>). Established cancer-causing mutations affect all of the major cellular regulatory processes described above, including alterations of histone modifications, DNA methylation, chromatin remodeling proteins, CTCF binding, transcription factor binding and/or expression, miRNA and lncRNA expression splicing, and the expression and/or activity of signal transduction proteins [4].

Fortunately, like any complex machine, cells engage multiple “back-up” systems whenever they incur a mutation in an oncogene or tumor suppressor gene. Consequently, 6-8 independent genetic changes must occur before a cell’s multiple failsafe mechanisms are breached and malignancy develops [5]. Typically, these include mutations in some combination of oncogenes and tumor suppressor genes. They also can include combinations of point mutations and structural variants, although most tumors are driven mainly by one or the other of these mutational processes. In some (but not all) types of cancer, “pre-malignant” lesions can be visualized under the microscope (histologically); DNA sequencing shows that such lesions have subsets of the mutations seen in full-blown cancers.

**Cancer is a genetic disease, but most cancer is not inherited:** All cancers are “genetic” (i.e., caused by mutations in (multiple) genes), but only a minority are “inherited” (i.e., caused by mutations that occur in a patient’s parents and are transmitted through the “germ cells” (sperm or eggs)) [6, 7]. Two general types of inherited variants contribute to increased cancer risk. Strong cancer risk often shows “autosomal dominant” inheritance, which means that inheriting one copy of the defective gene increases risk. Classic examples include: mutations of *BRCA1* or *BRCA2*, which increase susceptibility to breast and ovarian cancer, but also several other malignancies (pancreas, prostate, melanoma, etc.), *TP53* mutations, which cause “Li-Fraumeni syndrome,” and mutations in one of several genes involved in mismatch repair, which cause “Lynch syndrome.” Each of these can increase the risk of developing different types of ovarian cancer. Although germ line mutations typically show autosomal dominant inheritance, both copies of the gene usually must be inactivated for cancer to occur. Loss of the second copy (“allele”) can occur in multiple ways, including loss of all or part of the chromosome containing the normal copy, mutation, a process known as “gene conversion,” or epigenetic silencing of the chromatin containing the normal gene. Although *BRCA1* and *BRCA2* mutations show autosomal dominant inheritance, only some patients inheriting such mutations develop breast or ovarian cancer; hence, even these strong risk genes show “incomplete penetrance.”

Beyond strong cancer susceptibility genes, multiple single nucleotide polymorphisms (SNPs) each confer slightly increased risk of specific (or multiple) cancers [8]. SNPs, as their name implies, are variations in DNA sequence that occur between individuals. Most of these are normal variants that reflect the wide diversity of the human population; on average, any two unrelated individuals have a sequence difference approximately every 300 nucleotides (the total size of the human genome is 6 billion nucleotide pairs). Most SNPs are in non-coding regions, but protein-coding SNPs occur about every 900-1000 nucleotides. Although they are quite frequent, the overwhelming majority of SNPs have no pathological significance. Others, though, especially in combination, contribute to familial predisposition to cancer. Most risk-conferring SNPs have been identified by genome-wide association studies (GWAS), which simultaneously correlate large batteries of SNPs against different disease states. The most recent GWAS compendium lists ~100 SNPs that affect the risk of high grade serous ovarian cancer (<https://www.ebi.ac.uk/gwas/>). Notably, to be sure that SNPs are associated with a trait, one must correct statistics for multiple comparisons; i.e., the chance that if one measures enough parameters, some will seem to be associated by chance. Consequently, only SNPs that attain “genome-wide significance” are assured of association with cancer; genome-wide significance means a “P-value” of  $<10^{-8}$ .

Only 5-10% of cancers have a strong inherited predisposition (i.e., are due to inheritance of autosomal dominant risk alleles). Nevertheless, comparison of cancer incidence in identical and fraternal twins suggests that up to a third of all cancers have some familial component, with some cancers having even higher familial contributions. A recent large study of Nordic twins suggests that as much as 39% of ovarian cancer might have a familial component, although the error in this estimate is large (23-55%), and the study did not differentiate between different types of ovarian cancer [8].

Most cancer-causing mutations are “somatic,” meaning mutations occurring in non-germ (somatic) cells after birth. These result from DNA damage or errors in replication that exceed the

cellular repair capacity, occur sporadically, and accumulate over time. For this reason, the greatest contributor to cancer risk is age. Strong environmental “carcinogens,” such as cigarette smoke, X-rays and ultraviolet light, increase the rate of DNA damage, making it more likely that the damage will go unrepaired and result in a cancer-causing mutation. Agents that directly detect DNA damage can be detected by surrogate “genotoxicity” assays [9], such as the “Ames test.” Notably, however, even genotoxic compounds typically demonstrate a dose-response in their ability to cause cancer, for the simple reason that powerful cellular repair pathways are always attempting to reverse the damage that these agents cause. Because cells have this remarkable capacity to repair DNA, DNA damage is cumulative, and multiple genes must be mutated to generate a malignancy, the more exposure that one has to a genotoxic substance, the more likely one is to develop cancer. For example, the risk of lung cancer in cigarette smokers is related to “pack-years” (the number of packs smoked per day X number of years of smoking), and substantially increased risk is seen above 20 pack-years [10].

More recently, “mutational signatures” of several carcinogens have been discerned by DNA sequence analysis of tumors, which can reveal specific patterns of damage caused by these agents [11]. Agents or conditions that lead to increased inflammation can result in the production of “reactive oxygen species” (ROS), which can damage DNA and lead to mutations under certain conditions. Conditions like obesity, which is now the major risk factor for cancer in the United States, probably contribute to cancer at least in part by promoting inflammation and excess ROS generation. Nevertheless, the majority of cellular ROS are generated as part of normal physiological processes, particularly mitochondrial respiration [12]. Consequently, there is no reason to infer that a person who develops cancer has been exposed to a cancer-causing chemical or physical agent in the environment. Rather, most cancer-causing somatic mutations probably occur as a consequence of unrepaired errors in DNA replication, and are thus mere bad luck. Put another way, the cancer-causing environment is our own body – and the enemy lies within [13-16].

**Cancer disrupts normal cellular regulation:** When a cell has suffered a sufficient number of cancer-causing mutations, its normal function is disrupted in multiple ways, which differ for different types of cancer. In general, however, malignant cells share several “hallmarks” of cancer [5].

- Normal cells typically need external growth signals to proliferate. Cancer cells generate their own growth signals or become autonomous of external growth signals in other ways.
- Normal cells respond to external growth-inhibitory signals. Cancer cells ignore such signals.
- Normal cells self-destruct when they suffer DNA damage that is unrepairable. Cancer cells disable the self-destruct mechanism.
- Most normal cells divide only a limited number of times. Cancer cells can have markedly extended or even unlimited proliferative capacity.

- Normal cells replicate their genomes with high fidelity. Genomic integrity is compromised in cancer cells, and this lack of genome stability can result in ongoing genetic change and escape from therapy.
- Normal cells do not usually send signals to surrounding blood vessel cells to make new blood vessels. Tumors typically send multiple such signals, via a process known as tumor angiogenesis (the formation of new blood vessels). Angiogenesis enables tumors to create their own blood supply as they expand beyond their normal size and location.
- Normal cells typically are located within a defined area. For example, “epithelial cells” (the cells that line body tubes and cavities) usually rest on top of a “basement” membrane that separates them from underlying connective tissue and blood vessels. Cancer cells can invade through this basement membrane, and also can spread to, and establish residence in, other organs, a process known as “metastasis.”
- When normal cells express abnormal proteins – e.g., when they are infected with a virus or other pathogen – they display these proteins to the immune system, which can eliminate the cells. Cancer cells develop multiple strategies to evade the immune system.
- Normal cells typically have defining characteristics that make them look unique. For example, different cell types within the lung or gut have a distinct appearance under the microscope, because they have different functions. Cancer cells, to different extents, lose such “differentiated” features.
- Cancer cells often use fuels differently than normal cells, enabling them to survive in abnormal, and often hostile, milieus.

**Cancer is not a single disease – or even a single type of disease:** “Cancer” is not one disease, but probably hundreds. Pathologists sub-divide cancer in multiple ways. The simplest criterion is based on the type of cell from which the malignancy originates. Epithelia are the cells that line our body tubes and glands. Skin and the lining of our mouth, throat, lung, gastrointestinal tract, urinary tract, and reproductive organs, are composed of epithelial cells. “Carcinomas” are tumors that originate in epithelial tissues, and are then specified further by the (presumed) cell-of-origin (“breast” cancer, “lung” cancer, “bladder” cancer, etc.). “Sarcomas” initiate in connective tissue (mesenchymal) cells, such as bone (osteosarcoma), cartilage (chondrosarcoma), or striated or smooth muscle (rhabdomyosarcoma, leiomyosarcoma). Leukemias and lymphomas involve blood-forming cells. Pathologists also refer to “tumor grade,” which, as mentioned above, reflects the extent to which the tumor cell has lost the “differentiated features” of the cell-of-origin. High grade tumors resemble the normal tissue less than low grade tumors. A tumor’s “stage” typically reflects its size and the extent to which it has spread beyond its initial tissue boundary. Each tumor type has its own staging system, which usually goes from Stage I to IV. Staging, in turn, is based on the “**Tumor, Nodes, Metastasis**” criteria. For example, a Stage I ovarian cancer is confined to the ovary or fallopian tube, and has not spread to the lymph nodes, whereas a Stage IV tumor has spread beyond the pelvic cavity to other organs.

Although microscopic examination, grading and staging remain essential components of cancer diagnosis and therapy recommendations, with the advent of the molecular era, we realize that (microscopic) appearance isn't everything – in fact, it is relatively little. Instead, tumors from different organs can have similar molecular defects, whereas those from the same organ can be quite different. For example, high grade serous ovarian cancer is genetically – and functionally – more similar to triple negative breast cancer than to other types of ovarian cancer [17, 18]. These differences in the genetic architecture of different tumors also imply distinct underlying mutational processes. Stated simply, it is highly unlikely that tumors that have different genomic defects/mutational signatures are caused by the same mutational agent(s).

**Ovarian cancer is not a single disease – and in most cases, it is not even “ovarian”:** Even at the microscopic level, it is clear that ovarian cancer is more than one disease [19]. “Ovarian” tumors were initially thought to originate from one of the three cell types found within gonadal tissue: sex cord-stromal cells, germ cells and ovarian surface-epithelial cells. As described below, most “ovarian” tumors are now believed to originate from other tissues that implant on the ovarian surface early in their development as neoplasms. Nevertheless, the old histology-based nomenclature persists.

The vast majority (90%) of tumors of the ovary are “Epithelial ovarian carcinomas” (EOC) [19]. These, in turn can be sub-divided into high grade serous (~70%), mucinous (~3%), endometrioid (~10%), clear cell (10%) and low grade serous (<5%) carcinomas. The most common EOC, high grade serous ovarian carcinoma (HGSOC), is, unfortunately, also the most lethal gynecologic malignancy and the 5<sup>th</sup>-most-common cause of cancer death in women in the United States. The EOC subtypes differ in likely cell-of-origin, genomic abnormalities, metastatic potential, treatment response and therefore, prognosis. This disparity in their characteristics, and particularly, their distinct mutational profiles (see below), makes it almost certain that they differ in pathogenesis.

The remaining 10% of ovarian cancers comprise the germ cell and sex cord-stromal tumors, respectively. Germ cell tumors (~1-2% of all ovarian cancers) originate from defective germ cells or their derivatives (trophoblast, embryonal carcinomas). Sex cord-stromal tumors (~8-9% of ovarian cancer) arise from the tissues that surround and support the germ cells (granulosa cells, theca cells, fibocytes). Plaintiffs do not allege that talc causes this class of tumors, so I will not discuss them further.

**Epithelial ovarian cancers fall into two general classes:** Recent re-evaluation of EOC pathobiology suggest that these tumors should be re-classified into two large groups [20-22]. “Type I” tumors, which include low grade serous ovarian cancer (LGSOC), mucinous carcinoma (MC), endometrioid carcinoma (EC), and clear cell carcinoma (CCC), develop more slowly and through defined intermediate stages of differing malignant potential, are generally more genetically stable and less aggressive, and are usually detected at an early stage (Stage I). Increasing evidence also suggests that these tumors arise from different locations and cell types [22-26]. EC and CCC are thought to derive from endometriotic lesions from the uterus that implant on the ovarian surface and undergo further malignant transformation. LGSOC probably arises from fingertip-like projections (“fimbria”) at the ends of the fallopian tube (FT), although an ovarian surface epithelium (OSE) origin has not been excluded, and MC might arise from the

junction of the fallopian tube and the peritoneum (tubal-mesothelial junction) or from ectopic sites like the GI tract. Type II tumors comprise HGSOC, undifferentiated carcinomas and rare carcinosarcomas (the latter two are probably variants of HGSOC). At least 60% of these originate in the FT fimbria, and it is possible that they all do. HGSOC are highly aggressive, genetically unstable, and unlike Type I tumors, often appear without an obvious precursor lesion. However, close inspection of the fimbria can often (at least 60% of the time) reveal such a precursor, which is termed serous tubal intraepithelial carcinoma (STICs); indeed, it was the discovery of STIC lesions in *BRCA1/2*-mutant patients undergoing prophylactic removal of their fallopian tubes and ovaries that led to the FT “cell-of origin” concept [27-32].

Subsequent, detailed DNA sequencing studies of STICs and full-blown ovarian cancers have shown that in most cases, STICs contain only some of the genetic abnormalities seen in the bulk tumor [33, 34]. Scientists interpret such results as indicating that the STIC gave rise to the bulk tumor, arguing in favor of an FT origin for HGSOC. However, in other cases, tumors in the FT show more genomic changes than the ovarian mass, which suggests that the tumor-initiating event took place in (on) the ovary or elsewhere and then metastasized to the FT [35]. Furthermore, in the remaining 40% of HGSOC, no precursor lesion can be identified, leaving open the possibility that the tumor originated within the tumor mass(es) seen in the ovary. Comparison of gene expression in human normal ovarian surface epithelial cells, normal human fallopian tube epithelium (“FTE”), and a large panel of HGSOC indicates that a significant fraction (15-30%) of HGSOC appears more similar to OSE than to FTE [26]. Also, a recent study from our laboratory, which is under review (<http://biorxiv.org/cgi/content/short/481200v1>), shows unambiguously that either OSE or FTE can be transformed to generate HGSOC in mice. Thus, it is conceivable that not only do individual HGSOC cases have different combinations of mutations, but some might originate from the FTE, whereas others originate from OSE.

Finally, HGSOC, because it is often quite undifferentiated, or shows mesenchymal differentiation, can be difficult to discern from peritoneal mesothelioma under the microscope. Special immunohistochemical stains (e.g., for the marker PAX8) have made this differential diagnosis far more facile in modern pathology laboratories [36]. Nevertheless, mesothelioma originates from a distinct cell type (mesothelium), has distinct genomic abnormalities and likely has distinct causes. Whereas asbestos clearly causes pleural (chest wall) and peritoneal mesothelioma, this does not imply that it causes *bona fide* ovarian cancer.

**The different types of EOC are caused by distinct mutations and mutational types:**  
Type I tumors typically feature mutations in components of signal transduction pathways [20, 25]. For example, LGSOC and MC frequently have gain-of-function point mutations in *BRAF* or *KRAS*. *KRAS* and *BRAF* participate in the same signaling pathway downstream of most growth factor receptors, with *KRAS* functioning to activate *BRAF*. *KRAS* acts as a type of molecular “switch,” oscillating between an “on” *KRAS*-GTP state and an “off” *KRAS*-GDP state. When growth factors are present, *KRAS* is switched on, but then decays to the off state. Gain-of-function mutations cause *KRAS* to “lock” into the “on” state, so that the cell thinks that it is always getting a growth factor signal. *KRAS*-GTP binds to, and activates, *BRAF*. The gain-of-function mutations in *BRAF*-mutant Type I ovarian tumors render *BRAF* active in the absence of an upstream growth factor/*KRAS* signal. EC and CC often have loss-of-function mutations in *ARID1A*, which encodes a chromatin remodeling protein, activating mutations in  $\beta$ -catenin, a

transcription factor that mediates signals from WNT growth factors, and/or gain of function mutations in *PIK3CA* or loss-of-function mutations in *PTEN*. *PIK3CA* produces a signaling lipid, phosphatidylinositol-3-phosphate (PI3P), that is also evoked by growth factor signals, whereas *PTEN* encodes a protein (enzyme) that inactivates PI3P. EC can also be associated with Lynch syndrome, whereas the other Type I tumors show no such association. MC can have gain-of-function mutations in *KRAS* or *BRAF* or amplification of *HER2/ERBB2*, a growth factor receptor also amplified in 20% of breast cancer cases. *TP53* mutations are rare in Type I tumors, and they have relatively stable and “quiet” genomes, with few CNAs or rearrangements.

Type II tumors, by contrast, uniformly have *TP53* mutations or deletions [37], and reflecting *TP53*’s “guardian of the genome” role [38, 39], these tumors look as if a bomb has been dropped in their genomes [40]. There are multiple CNAs, including amplifications, deletions, translocations and fusions. HGSOC cells are highly aneuploid (i.e., have the wrong number of chromosomes) and also have multiple epigenetic changes from normal FT cells. As noted above, up to 10% of HGSOC patients have germline *BRCA1* or *BRCA2* mutation, but *BRCA1/2* are somatically mutated or epigenetically silenced in up to 20% of HGSOC. Other frequent mutations include *PTEN* deletions, *PIK3CA* or *KRAS* amplifications (although point mutations in these genes are rare, unlike in Type I tumors), *NOTCH3* (a type of receptor) or *CYCLIN E* (and cell cycle regulator) amplification and *FOXM1* (a key transcription factor) deletions.

The high degree of genomic abnormality and instability in HGSOC reflects the mutations that are found in this disease. *TP53*, as mentioned before, is often termed the guardian of the genome because of its critical role in maintaining genomic integrity [38, 39]. When *TP53* is defective, multiple genomic abnormalities can accumulate without the cell receiving a “self-destruct” signal. *BRCA1/2* play critical, direct roles in a specific type of DNA repair, termed homologous recombination repair (HRR) [41]. When cells are defective in HRR, they resort to back up, mutation-causing pathways [42].

Taken together, these findings clearly show that different types of ovarian cancer originate in different cell types that suffer different types of mutations, which are unlikely to be caused by the same environmental agent. *Studies, including epidemiological reports, that treat “ovarian cancer” as a single entity, should, in my opinion, be viewed with skepticism.*

**Multiple factors, rather than a single cause, likely contribute to ovarian cancer generation:** It is difficult to attribute a specific case of cancer to a single cause. Even in smokers, lung cancer is not inevitable, as we know from individuals who have smoked for many years and yet have not developed cancer. Rather, for any cancer, it is only meaningful to speak in terms of exposures that increase risk. It is also important to quantify such risks if it is possible to do so in a scientific way. Risk factors can generally be grouped into genetic and environmental factors. Not surprisingly, both types of risk factors differ for different types of tumors. Moreover, given the multiple lines of evidence, discussed above, that ovarian cancer arises in different cell types as a consequence of distinct mutational events, it should be equally unsurprising that different subtypes of the disease are associated with different risk factors.

It is also important to distinguish *association* between a risk factor and a disease, and a demonstrated causal association. The former means that two events occur more frequently than expected by chance, whereas the latter means that one event causes the other. Two events can occur in common and not be causally related, if one event occurs in association with an undefined causal association. For example, one might find an association between a baby drinking juice and the incidence of a certain disease, and jump to the conclusion that the juice is causing the disease. However, it could be that the juice is almost always imbibed from a plastic bottle and, by virtue of its acidic character, causes other disease-evoking agents to leak from the plastic. To truly demonstrate a causal association requires a plausible, demonstrable biological mechanism of disease. In other words, one must avoid attributing guilt by association to fellow travelers.

There are several clearly established risk factors for all ovarian cancer, and others for specific types (reviewed in [43]). As for almost all cancers, age is a major risk factor: the older a woman is, the more likely she is to accumulate the mutations that lead to ovarian cancer. Genetic risk factors for ovarian cancer were described above and will only be reiterated briefly here. Strong risk is conferred by mutations in *BRCA1* (44% lifetime risk, compared with 1.3% overall), *BRCA2* (27% risk), or other genes involved in HRR (e.g., *BRIP1*, *RAD51C*, *RAD51D*; 5-12% lifetime risk each). These mutations predominantly increase the risk of HGSOV. Lynch syndrome mutations are associated with EC and CCC. Risk SNPs also contribute, but even including these, based on the aforementioned twin studies, less than half of the familial risk can be assigned at present. Nevertheless, in predicting any individual's risk of developing ovarian cancer, these genetic contributions must be considered.

Endometriosis is a risk factor, but only for CC and EC, reflective of the currently accepted pathogenic mechanisms for these diseases (reviewed in [43]). Parity (giving birth) is among the best accepted protective factors. Two major hypotheses have been proposed to explain these observations: incessant ovulation and the gonadotrophin hypothesis. With every ovulation event, there is damage to the OSE that must be repaired; the incessant ovulation hypothesis holds that mistakes can be made during this repair process, leading to mutations. Ovulation is also proposed to damage the FTE fimbria, accommodating the more recent evidence that FT is the site of origin for HGSOV and LGSOC. The gonadotrophin hypothesis argues that luteinizing hormone (LH) and/or follicle stimulating hormone (FSH), rather than ovulation *per se*, can stimulate the relevant target cells to undergo transformation. Early menarche, nulliparity and late menopause, all of which lead to longer periods of unopposed menstrual cycling, are often said to be associated with increased risk of ovarian cancer (reviewed in [43]). However, there are conflicting studies on this issue, and overall, the effect is likely to be small. Infertility might also increase risk, although "infertility" has multiple causes, only some of which might be relevant. Also, it can be difficult to distinguish the effects of infertility from the effects of drugs used to treat this condition. Conversely, the use of oral contraceptives reduces risk. Because LH and FSH direct the normal menstrual cycle, it is difficult to distinguish between these models, as increased exposure to LH and FSH occur together with ovulation in women who have early menarche, late menopause or nulliparity. Regardless, it should be noted that neither of these proposed mechanisms requires any external agent to promote cancer development.

Certain gynecologic procedures or therapies also affect the risk of ovarian cancer. Some studies indicate hysterectomy may reduce risk and bilateral tubal ligation reduces risk by approximately 20-30%, although risk reduction is greatest for EC and CCC, consistent with their proposed pathogenesis (reviewed in [43]). Bilateral oophorectomy markedly lowers risk, which might seem tautological at first, but need not be if the cell-of-origin for different types of OC is not the OSE. Rather, these findings suggest that some factor in the ovaries or the ovarian environment itself is necessary for cancer to develop. Conversely, post-menopausal hormone therapy, especially with estrogen alone, increases risk, with the increase in risk possibly greater for EC and CCC. Whether combined estrogen/progestin also increases risk is less clear, and in any event, the magnitude of the increase is likely to be less.

Finally, lifestyle factors can affect the risk of some subtypes of ovarian cancer. Obesity increases the risk for non-HGSOC, and smoking increases the risk of MC, but has no apparent effect on other subtypes. All of these factors are relevant to individual risk, and it is difficult to control them all when comparing two patient populations. This difficulty, in turn, makes it hard to interpret apparent small increases in risk in epidemiologic studies, particularly when the results of such studies are inconsistent.

### III. TALC AND OVARIAN CANCER

**Opinion: Talc is not genotoxic, does not cause mutations, does not cause inflammation in the female genitourinary tract and has not been shown to cause ovarian cancer.**

**Talc is chemically inert and non-genotoxic:** Talc is a plate-like magnesium silicate that is chemically inert. It does not score as positive (i.e., cause mutations) in standard genotoxicity assays [44]. Talc is present ubiquitously in foods, such as chewing gum, candies, cured meat, olive oil, ceramics, papers, inks, soaps, plastics, cosmetics and other products [44]. The FDA regulates talc and rejected proposals to add ovarian cancer warnings as recently as 2014 (Letter from Food & Drug Admin., Dep't of Health & Human Servs., to Samuel S. Epstein, M.D., Cancer Prevention Coalition, University of Illinois - Chicago School of Public Health (Apr. 1, 2014)). The IARC reviewed the literature on talc in 2010 and classified it as “possibly carcinogenic (class 2B),” which, according to its definition, means that “there is limited evidence of carcinogenicity in humans *and* less than sufficient evidence of carcinogenicity in experimental animals.” (Int'l Agency For Research On Cancer, World Health Org., *93 Monographs on the Evaluation of Carcinogenic Risks to Humans: Carbon Black, Titanium Dioxide, and Talc* at 35 (2010).) Very recently, Health Canada again reviewed the literature surrounding talc and ovarian cancer, stating in a draft screening assessment that talc was “possibly carcinogenic” [45]. I carefully reviewed the Taher et al. manuscript that was funded by Health Canada, which is under review for publication but has been released to the public. It focuses primarily on a meta-analysis of the numerous epidemiological studies on the topic of talc and ovarian cancer, noting that 63% show a positive association, while 37%, including the strongest cohort studies, show no association. In my opinion, the studies cited by this report are weak and unconvincing (see below).

**There is no compelling evidence that talc causes ovarian cancer:** Multiple lines of evidence are needed to convincingly show that a given agent is carcinogenic. These have been

standardized into specific criteria, known as the Bradford Hill criteria [46].

1. **Strength of association:** Multiple epidemiologic studies have investigated a possible relationship between talc and *any* type of ovarian cancer. As discussed above, it is not biologically meaningful to lump together all ovarian cancer subtypes, as they arise from different cells-of-origin, distinct genetic events and therefore, different types of DNA damage/repair problems. Even so, the epidemiological studies have been inconsistent, and the purported effects, even when present, are small. A recent “meta-analysis” (aggregate analysis) included 24 case-control and three cohort studies, and found an association between “any perineal use” of talc (including use on diaphragms and sanitary napkins) and ovarian cancer with an odds ratio (OR) of 1.31 [47]. When the entire meta-analysis was considered, risk was only increased for HGSOC and EC. Based on their distinct pathogenesis, however, it is not clear why only these two subtypes showed increased risk. In particular, as discussed above, CCC and EC arise in endometrial cells and have similar mutational spectra. It is unclear why one, but not the other, would show an increase, if women were exposed to the same pro-cancer agent. Similar conclusions were reached in meta-analyses by Berge *et al.* [48], and by the aforementioned Health Canada review [45].

Notably, cohort studies fail to find an increased risk of ovarian cancer overall with “any use” of talc. In their meta-analysis, Berge *et al.* [48] note that, based on the combined number of cases and controls in the cohort studies, the statistical power to detect an association in these studies, when pooled, should have been 99%. The pooled cohort studies do report a small increase in HGSOC for ever use of talc (OR 1.25). This increase is quite small, though; by comparison, smoking causes a 25-fold increase in risk of lung cancer. (See Smoking and Cancer, [https://www.cdc.gov/tobacco/data\\_statistics/sgr/50thanniversary/pdfs/fs\\_smoking\\_cancer\\_508.pdf](https://www.cdc.gov/tobacco/data_statistics/sgr/50thanniversary/pdfs/fs_smoking_cancer_508.pdf).) When an effect is so small, it is difficult to rule out other potential contributors to ovarian cancer, or HGSOC, risk. For example, a major weakness of all of these studies is that the talc exposures are self-reported, and therefore accurate quantification of exposure is difficult. Also, exposures occurred via different routes, and the various studies did not find that routes of exposure were equivalent. Alternatively, some other practice or exposure that is not routinely queried might be more common in talc users. Furthermore, none of these studies restricted themselves to the products at issue in this litigation (Johnson’s Baby Powder and Shower to Shower), and therefore any conclusion about the products at issue is inherently confounded.

2. **Consistency of Relationship:** As noted above, the individual epidemiologic studies do not show a consistent relationship between talc and ovarian cancer, and the meta-analyses show differences between the population-based case-control studies and the cohort studies. The case-control design attempts, as best as possible, to match cases to individuals who share the same characteristics except the disease under study. However, because a patient knows she has the disease, case-control studies can be confounded by “recall bias.” For example, if news reports indicate a possible connection between talc exposure and ovarian cancer, recollections can be different. The finding of a higher relative risk in more recent case-control studies, compared with earlier ones [49, 50], is consistent with this potential problem, as noted by Berge *et al.* [48]. In the latter study, for example, an association with “ever use” was only seen for patients interviewed after 2014, when there was already substantial

publicity about a potential talc/ovarian cancer connection. The authors of the study explicitly acknowledge the possible influence of litigation, but nevertheless, such influence seriously confounds any conclusion that talc caused the ovarian cancers seen in these women. Also unclear is why hospital-based case-control studies fail to detect an association whereas population-based reports do detect one, again suggesting that these studies might not be capturing all relevant variables [45, 48, 51]. The case-control studies also are inconsistent regarding exposure route. Some see an increase in ovarian cancer incidence in women exposed by “any route” [50, 52]. Notably, exposure via talc on condoms or diaphragms, which one might expect to introduce particles to the upper genitourinary (GU) tract (i.e., the area of the body encompassing the reproductive organs) more proximately than perineal dusting, did not show increased risk when queried [45, 47, 48]. Also, different studies are heterogeneous regarding the source of talc, the inclusion or exclusion of other powders, other queries about other potential confounding factors (e.g., douching [53]) and the extent of genetic risk data collected [45].

3. **Biological Plausibility:** For an agent to be adjudged the cause of cancer, there must be a demonstration of a plausible biochemical mechanism. In my opinion, there simply are no compelling data to this effect. As noted above, talc is universally acknowledged to be non-genotoxic in standard mutagenesis assays. The plaintiffs’ experts cite several alternative mechanisms by which talc could be cancer-promoting, but the evidence supporting each of these mechanisms is quite weak, as detailed below:

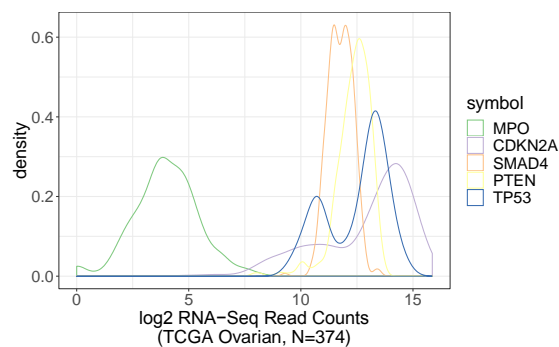
**Route of access:** The plaintiffs’ experts argue that talc can be transported from the vagina through the cervix to the uterus and into the fallopian tube, ovary and peritoneum. No data are available relating perineal exposure to exposure in the relevant target tissue. It simply is not clear whether talc can regularly get from the perineal area to the region of the fallopian tube or the ovarian surface epithelium, and even if it can, the relationship between the amount of talc applied to underwear or sanitary napkins and the amount that reaches the relevant cells is completely unclear. The plaintiffs’ experts do not identify any convincing, direct evidence on this point. Instead, they cite to earlier papers to support this hypothetical possibility. For example, Egli and Newton [54] placed inert dextran particles via a speculum into the posterior fornices of the vagina of three women undergoing elective hysterectomy (and thus under general anesthesia). They then administered 10U of oxytocin, rapidly placed the patient in the supine, flat position, retrieved the fallopian tubes, and found particles in 2/3 within 28-34 min. It should be obvious that the design of this study bears little resemblance to the standard ways that women use talc in the perineal area. Furthermore, the above study is seriously compromised by its small size, use of anesthesia and oxytocin (which causes uterine contractions), and lack of information regarding the relative dose of these particles compared to what might be reasonably expected to be a dose of talc from perineal dusting. These authors argue for the physiological relevance of the oxytocin administration, as oxytocin is released during intercourse. In that case, one might expect that talc on diaphragms or on condoms would show the largest association with risk in the epidemiological studies. However, as mentioned above, the epidemiological studies find exactly the opposite. Venter and Iturralde [55] deposited radioactively labelled albumin microspheres into the posterior fornices of 24 patients one day before different operations. Only 21 cases could be examined (in the other, the particles streamed out of the vagina), and

16 showed radioactivity reaching the uterus or higher. This study is also compromised by a lack of clear relevance between depositing large numbers of particles in the posterior fornix versus perineal dusting of talc.

By contrast, Heller *et al.* [56] examined the ovaries of 24 women undergoing incidental oophorectomy, and collected data on talc use. Twelve women reported frequent perineal talc application; the other 12 reported no use. Blocks of ovarian tissue were digested and examined by polarized light microscopy and electron microscopy. Talc was detected in all 24 patients, regardless of exposure. Although these data show that talc can be found at high frequency within ovarian tissue, they argue strongly that perineal talc use does not accurately reflect potential exposure. Similarly, Henderson [57] found talc in 10/13 ovarian tumors, 12/21 cervical tumors, and 5/12 normal ovaries. There was no correlation between particle count and patient-reported talc exposure. Together, these findings, which would appear to be directly on-point, vividly illustrate the unreliability of conclusions based solely on epidemiological studies that rely entirely on self-reporting of talc exposure. Furthermore, no evidence of inflammation, fibrosis or other forms of damage to the ovaries or FT was reported by either Heller *et al.* or Henderson.

**Purported carcinogenic mechanism:** Talc is not genotoxic in standard mutagenicity assays in lower organisms, has never been shown to induce mutations in any cancer-causing gene (oncogene or TS gene) in human cells, and has not been shown to cause CNAs in any setting. Plaintiffs' expert, Dr. Saed, argues that talc promotes cancer by inducing oxidative stress, which in turn could be mutagenic. He provides several potential mechanisms by which this could occur, much of it based on his own work. In my opinion, these studies are technically and conceptually flawed, and do not withstand critical scrutiny. I will discuss each of these claims below:

- a) “[O]varian cancer patients manifest significantly decreased levels of antioxidants and higher levels of oxidants” (p. 5). Regardless of whether this statement is true, it is a *non-sequitur* insofar as ovarian cancer pathogenesis is concerned. By the time a patient has developed obvious ovarian cancer, one cannot determine whether the above phenomena are cause or effect. Dr. Saed provides no evidence on the oxidation state of *pre-malignant* lesions, which is when a carcinogen that promotes inflammation would be expected to act.
- b) “MPO . . . and iNOS . . . are highly expressed and co-localized . . . in EOC cells” (p. 5). Again, even if this statement were true, it too is a *non-sequitur*, for the reasons discussed above. Indeed, the claim that MPO is not expressed in normal ovarian epithelium, if anything, argues against any purported involvement in talc-mediated ovarian carcinogenesis. I have reviewed the paper that Dr. Saed quotes (from his own laboratory) to support this claim, and find it seriously flawed at multiple levels. First, he uses one cell line (SKOV3) that is not representative of HGSOC [58] and another of uncertain provenance. Since the focus of many of plaintiffs' experts is on the potential association between talc and HGSOC, which is also the most common form of ovarian cancer, these cell lines are irrelevant. Second, he uses immunostaining methods to identify MPO, but fails to provide key controls for his reagents. This shortcoming is no trivial matter, given



**Figure 1:** RNA-sequencing counts for *MPO*, compared with known ovarian cancer TS genes, showing virtually undetectable expression of the former in 374 HGSOC. Raw data available at: [www.portal.gdc.cancer.gov](http://www.portal.gdc.cancer.gov).

that *MPO* is only known to be expressed in myeloid cells, and inspection of the Cancer Cell Line Encyclopedia (CCLE) database (<https://portals.broadinstitute.org/ccle>) reveals no significant *MPO* mRNA expression in cell lines other than those of myeloid origin. Likewise, inspection of The Human Cancer Genome Atlas data on HGSOC shows that *MPO* RNA is virtually undetectable; notably, its levels are lower than those of standard ovarian cancer TS genes (Figure 1). Most likely, the low residual counts reflect *MPO* expression in infiltrating myeloid cells rather than, as claimed by Dr. Saed, tumor cell expression. Third, his functional

experiments, involving a technique known as RNA interference (RNAi), lack standard controls. In RNAi experiments, scientists introduce short double stranded sequences (siRNAs) into cells. These siRNAs can direct the degradation of mRNAs that contain this sequence, but the technique is not absolutely specific. Instead, a given siRNA can gratuitously degrade other mRNAs, a phenomenon we term “off-target” effects. All high-quality journals require that such controls be performed; yet, they were not done in Dr. Saed’s paper.

- c) “Common SNPs in the redox enzymes are known to be strongly associated with altered enzymatic activity . . . that has been linked to . . . ovarian cancer” (p. 7-8). It is true that a SNP in *GPX6*, which encodes a redox enzyme, is associated with HGSOC risk, although notably, Dr. Saed does not mention this SNP. The ones that he does discuss either do not reach genome-wide significance (and thus are not conclusively associated with ovarian cancer risk) or are associated with other biological processes. **See Appendix A.** For example, the only SNPs in the catalase gene (*CAT*) that reach genome-wide significance affect blood catalase levels, whereas *MPO* SNPs are associated with blood levels of this enzyme or with white blood cell levels (<https://www.ebi.ac.uk/gwas/genes/MPO>). **See Table 1 (adapted from <https://www.ebi.ac.uk/gwas/search?query=mipo>).**

**Table 1 – GWAS Associations For *MPO* That Reach Genome-Wide Significance  
(Note Lack of Ovarian Carcinomas)**

Disease/Trait	Region	Reported Gene	Mapped Gene	Source
Circulating myeloperoxidase levels (plasma)	17q22	<i>MPO</i> , <i>RNF43</i> , <i>PPM1E</i>	<i>MPO</i> - <i>BZRAP1</i>	Reiner AP. Genome-wide and gene-centric analyses of circulating myeloperoxidase levels in the charge and care consortia. Hum Mol Genet. 2013 Aug 15;22(16):3381-93.

Disease/Trait	Region	Reported Gene	Mapped Gene	Source
Blood protein levels	17q22	NR	MPO	Sun BB. Genomic atlas of the human plasma proteome. Nature. 2018 Jun;558(7708):73-79.
Blood protein levels	17q22	NR	MPO	Sun BB. Genomic atlas of the human plasma proteome. Nature. 2018 Jun;558(7708):73-79.
Blood protein levels	17q22	MPO	MPO - BZRAP1	Sun BB. Genomic atlas of the human plasma proteome. Nature. 2018 Jun;558(7708):73-79.
Post bronchodilator FEV1/FVC ratio in COPD	17q22	MPO	MPO	Lutz SM. A genome-wide association study identifies risk loci for spirometric measures among smokers of European and African ancestry. BMC Genetics 2015 16:138.
Monocyte count	17q22	MPO	MPO - BZRAP1	Astle WJ. The Allelic Landscape of Human Blood Cell Trait Variation and Links to Common Complex Disease. Cell. 2016 Nov 17;167(5).
Monocyte percentage of white cells	17q22	MPO	MPO - BZRAP1	Astle WJ. The Allelic Landscape of Human Blood Cell Trait Variation and Links to Common Complex Disease. Cell. 2016 Nov 17;167(5).
Granulocyte percentage of myeloid white cells	17q22	MPO	MPO - BZRAP1	Astle WJ. The Allelic Landscape of Human Blood Cell Trait Variation and Links to Common Complex Disease. Cell. 2016 Nov 17;167(5).
Neutrophil percentage of white cells	17q22	MPO	MPO	Astle WJ. The Allelic Landscape of Human Blood Cell Trait Variation and Links to Common Complex Disease. Cell. 2016 Nov 17;167(5).
Myeloid white cell count	17q22	MPO	MPO	Astle WJ. The Allelic Landscape of Human Blood Cell Trait Variation and Links to Common Complex Disease. Cell. 2016 Nov 17;167(5).
Granulocyte	17q22	MPO	MPO	Astle WJ. The Allelic Landscape of

Disease/Trait	Region	Reported Gene	Mapped Gene	Source
count				Human Blood Cell Trait Variation and Links to Common Complex Disease. Cell. 2016 Nov 17;167(5).
Sum neutrophil eosinophil counts	17q22	MPO	MPO	Astle WJ. The Allelic Landscape of Human Blood Cell Trait Variation and Links to Common Complex Disease. Cell. 2016 Nov 17;167(5).
Sum basophil neutrophil counts	17q22	MPO	MPO	Astle WJ. The Allelic Landscape of Human Blood Cell Trait Variation and Links to Common Complex Disease. Cell. 2016 Nov 17;167(5).
Neutrophil count	17q22	MPO	MPO	Astle WJ. The Allelic Landscape of Human Blood Cell Trait Variation and Links to Common Complex Disease. Cell. 2016 Nov 17;167(5).
White blood cell count	17q22	MPO	MPO	Astle WJ. The Allelic Landscape of Human Blood Cell Trait Variation and Links to Common Complex Disease. Cell. 2016 Nov 17;167(5).

Furthermore, the fact that alterations in redox state might contribute to ovarian cancer risk implies nothing about whether talc is oncogenic; nor does it imply that talc is in any way associated with redox state in the fallopian tube or ovarian surface epithelium.

- d) “*Chemoresistance is Associated with Point Mutations in Key Redox Enzymes in EOC cells*” (p. 9). Again, this entire line of reasoning is not germane to the issue of talc and ovarian cancer. Also, HGSOC is a disease of CNAs, not point mutations (see above).
- e) “[T]alc . . . initiates a[n] . . . inflammatory response” (p. 10/11). There simply is no compelling evidence that talc induces an inflammatory response in the female genital tract. Notably, no evidence of inflammation was reported in studies that documented talc in surgical tissue from women undergoing oophorectomy (see above). In other words, when the putatively offending substance has been found in the site in which ovarian cancer develops, there have been no evident pro-inflammatory *effects*!
- f) “*Studies that exposed lab animals (rats, mice, hamsters) to asbestos-free talcum powder in various ways have had mixed results*” (pp. 10-11). Here, it is unclear to what Dr. Saed is referring, as he cites two epidemiology papers, not biology experiments. ***In fact, no***

*animal studies have shown that ovarian cancer develops following talc injection.*

- Hamilton *et al.* [59] injected talc directly into the rat ovarian bursa (the junction of the FT and the ovary). *They specifically noted that no malignancies were observed.* They also did not report evidence of STIC, the well-accepted precursor lesion for HGSOc, as discussed above. Focal papillary changes were seen in the OSE, but the authors noted that these changes could be due to high concentrations of hormones that accumulated in the intrabursal space due to the amount of talc injected. They also specifically noted *no evidence of inflammation*, although foreign body granulomas were seen. Importantly, granulomas are *not* observed during human ovarian cancer development (e.g., in patients with STICs). Moreover, the doses that were injected were massive (100 ul of 100 mg/ml talc suspension). The authors concluded that their results were “preliminary,” and notably, they never published on this topic again. Nevertheless, the fact that these massive amounts of talc failed to show any evidence of pro-oncogenic effects is strong evidence against plaintiffs’ experts’ arguments.
  - Keskin *et al.* [60] delivered talc to rats intravaginally or via their perineum. They also observed foreign body reactions (granulomas), as well as infections, in both groups exposed to talc, but *no neoplastic changes*. They concluded that talc causes foreign body reaction and infection, but not cancer.
- g) “*Migration/transport of particles through the genital tract is universally accepted*” (p. 11). Again, as discussed above, the evidence supporting this notion is far from “universally accepted”; to the contrary, it is actually quite limited. Furthermore, this mechanism fails to explain the frequent finding of talc particles in normal ovaries of women with no self-reported talc exposure. In its report evaluating the potential carcinogenicity of talc, IARC specifically noted that the evidence for transport was weak [44], whereas the recent Health Canada study maintained that data on talc migration were “inconsistent [45].”
- h) “[T]he inflammatory nature of talcum powder [is] consistently demonstrated” (p. 11). Notwithstanding this strong statement, the evidence simply fails to support this claim. As noted above, injection of large amounts of talc into the relevant organs in experimental animals does NOT cause inflammation other than granulomas, much less neoplasia. Similarly, there is no evidence of any type of inflammation – including granulomas – in women with documented talc particles in their ovaries (see above). Dr. Saed cites a paper by Shukla *et al.* [61] in which human mesothelial cells were exposed to talc for eight and 24 hours, respectively, and some changes in *gene expression* were noted. This study examines a cell type (immortalized pleural mesothelial cells) that is not directly relevant to ovarian cancer pathogenesis, and even then, reports quite minor changes in gene expression. The same study included limited studies on immortalized OSE cells, but found almost no significant changes in gene expression. As discussed above, OSE also is likely not to be the target cell for most HGSOc, and even if it were, there is no evidence that talc causes anything other than granulomas, which are not typically associated with

human ovarian cancer and are seen in animals only at exceedingly high doses of talc instillation.

- i) “*Findings from recent research from [the Saed] laboratory*” (p. 13). Dr. Saed provides a manuscript in press and several abstracts purporting to show changes in the levels of certain redox enzymes in response to talc exposure, including exposure to Johnson’s Baby Powder. Even if one were to accept these data at face value, the mere finding of differences in the levels of certain redox enzymes does not alone provide evidence of an altered redox state within cells, much less a pro-oncogenic effect of talc. Notably, Dr. Saed fails to carry out standard measurements to assess intracellular ROS and/or their effects, such as DCF fluorescence (to measure H<sub>2</sub>O<sub>2</sub> levels), BODIPY staining (to assess lipid peroxidation) or measurement of 8-oxo-dG in DNA (measurement of oxidative DNA damage). Also, these short-term assays in no way model what he claims throughout his report to be “chronic inflammation” induced by talc. It bears repeating that experimental animals and, most importantly, women, with documented talc exposure show no neoplastic changes, nor is there any evidence that talc evokes changes in redox state *in vivo*. Furthermore, it should be noted that careful examination of Dr. Saed’s laboratory notebooks reveals inconsistencies with the data in his abstract and manuscript, whited out sections, removal of some data points as “outliers” for unclear reasons, and the use of single biological replicates for each of the talc doses tested.
- j) In his manuscript, Dr. Saed also makes the truly extraordinary claim that “talc treatment was associated with a genotype switch” for SNPs in redox enzymes (Manuscript p. 7, 11; Report p. 19). What this means is that a specific base in DNA (“letter” in the DNA code) is somehow specifically changed in nearly 100% of the cells treated with talc, an agent that he acknowledges is not directly genotoxic! Even if talc were mutagenic (i.e., capable of inducing changes in the DNA code) – for example, by generating DNA-damaging ROS – such damage would be random, not affecting a specific base that just happened to be part of a SNP. It would be totally unprecedented for any agent to cause a switch in genotype at a specific locus, and Dr. Saed not only provides no mechanism to explain this claim, he does not appear to recognize just how extraordinary such a claim would be. Of note, I inspected the printouts for the SNP analysis in Dr. Saed’s lab notebooks, and several are technically flawed, making it difficult to be confident of the allele (“letter”) assignment. He could have easily confirmed these assignments by direct Sanger sequencing of the DNA, but did not do so. Simply stated, the reference to “talc treatment-induced gene point mutations” is not credible.

Dr. Saed’s in-press manuscript was previously rejected at the (higher quality) journal *Gynecologic Oncology*. Reviewer 1 of the initial manuscript noted that the paper’s claim that “‘oxidative stress is a key mechanism to the initiation and progression of ovarian cancer’ is not supported by this investigation.” I share that view. Similarly, Reviewer 2 noted that, “their data do not show, despite the authors’ claim, any evidence that these cells are transformed (i.e., malignant).... Consequently, neither tumor initiation nor progression is documented in this study, as opposed to the statement in Highlight #1 (in the text) and elsewhere. While changes in redox potential play an important role in tumor biology in general, the present data are insufficient to back up the claim that talcum (sic)

is central to the development of ovarian cancer.” I also share Reviewer 2’s view.

- k) Dr. Saed’s deposition testimony contains several statements that call into question his knowledge of basic cancer cell biology, genetics and biochemistry. For example, he states that p53 is an oncogene, whereas it is a paradigmatic tumor *suppressor* gene (p. 230). He states that cells are grown at normal oxygen and glucose levels (pp. 252-257), whereas in fact, they are typically grown at ~3X normal oxygen levels and 4X normal glucose concentrations. He does not appear to know that GWAS aggregates all published work on SNPs associated with disease risks and traits (pp. 205-206). His comments on SNPs in the catalase gene (p. 206-207) call into question his understanding of linkage disequilibrium, the concept that blocks of SNPs located close together in the genome are typically co-inherited. He does not appear to understand that the BCA assay is a colorimetric assay, rather than a direct measurement of absorbance (pp. 119-120). He does not seem to be aware of recent evidence that full-blown cancers are often more sensitive to oxidative stress [12]; indeed, one therapeutic approach under investigation in several laboratories is to promote increased oxidative stress in cancer cells. He states that CA125 is a marker of inflammation (p. 248), but this statement too is speculative. He states that normal cells have a higher apoptotic rate than cancer cells. Healthy normal cells do not have a higher apoptotic rate than cancer cells, although unhealthy or damaged normal cells are more likely to undergo apoptosis than cancer cells. Perhaps most importantly, none of Dr. Saed’s contentions or conclusions is based on animal studies, much less on human data.
- l) *Relationship between MUC1 antibodies and ovarian cancer pathogenesis (Zelikoff report, p. 19).* Plaintiffs’ expert Dr. Judith Zelikoff cites work showing that talcum powder users have lower plasma levels of MUC1 antibodies than non-users [62], and proposes that decreased immunity to MUC1 could be a mechanism by which talc increases ovarian cancer risk. Anti-tumor immunity is primarily mediated by anti-tumor T lymphocytes and possibly NK cells [63]. Because there is no evidence that anti-MUC1 antibodies (which are produced by B-lymphocytes) play any role in immune surveillance of ovarian or other types of cancer, this opinion should be viewed as pure speculation.
- m) *“Recent clinical and prospective data suggest that C-reactive protein (CRP), a marker of global inflammation, is associated with increased ovarian cancer risk” (Zelikoff, p. 20).* Dr. Zelikoff cites work by Poole [64], who measured the association of various inflammatory markers and ovarian cancer development in the Nurse’s Health Studies 1 and 2 and the Women’s Health Study (WHS). This study showed a 53% increase in risk for ovarian cancer for women with the highest (4<sup>th</sup>) quartile, compared with the lowest (1<sup>st</sup>) quartile, CRP levels in the blood. Notably, there was no association with IL6 (a cytokine marker of inflammation) or secreted TNF $\alpha$ R2 levels (another inflammatory marker). This study, as well as work by Trabert *et al.* [65], shows that some degree of systemic inflammation may be present during the development of ovarian cancer. However, a recent analysis of 26 STIC and early serous carcinomas saw no evidence of inflammation [66]. Moreover, NHS-1 and the WHS collected talc exposure data – indeed, these are among the major cohort studies of the talc/ovarian cancer association. Yet, while they could have addressed this key question, neither Poole *et al.* nor Trabert *et al.*

analyzed the relationship between perineal talc exposure and inflammation. Hence, there simply is no evidence in these papers that links perineal talc exposure to inflammation, whereas, as mentioned above, direct experiments argue against any such link. It also remains possible that increased CRP is a sign of inflammation that results from, rather than causes, ovarian cancer, a possibility acknowledged by Poole *et al.* Notably, a subsequent meta-analysis of this issue concluded that “Further studies are needed to definitively identify the role of CRP in the etiology of ovarian cancer [67].”

n) *Effect of talc on macrophages and relevance to ovarian cancer.* In her report, Dr. Zelikoff (pp. 22-24) raises the possibility that talc ingestion, either directly or on lipid particles, might have pro-inflammatory effects on macrophages. In fact, the picture that emerges from the papers she cites is complex, confusing and in some cases contradictory. In no way does the evidence cited by Dr. Zelikoff rise to the level of scientifically conclusive.

- **Bogatu and Contag** [68] argue that talc binds to high-density lipoprotein particles, which are then ingested into macrophages. Dr. Zelikoff notes that this could trigger a fibrogenic reaction (scar formation). However, there is no evidence for the involvement of scarring/fibrosis in ovarian carcinogenesis. Furthermore, there was no evidence of scarring in ovaries in which talc particles were detected. Indeed, Bogatu and Contag’s focus was on mechanisms underlying silicosis, not ovarian cancer.
- **Ghio *et al.*** [69] report that mineral talc sequesters iron (Fe) from cells, resulting in increased Fe uptake, oxidative stress and ROS production. This study involved immortalized bronchial epithelial and primary pleural mesothelial cells, which are not obviously relevant to ovarian cancer. Furthermore, there is no evidence that injecting talc into the pleural space causes lung cancer or mesothelioma.
- **Akhtar *et al.*** [70, 71] measured the effects of talc on A549 cells, and found ROS production, oxidation of cellular lipids and DNA damage. The relevance of this work to ovarian carcinogenesis also is extremely questionable. Because A549 are lung cancer cells, they are from an irrelevant cell-of-origin and are already malignant. In addition, it is not clear how the doses seen here relate to the small number of particles in the female reproductive tract.
- **Davies *et al.*** [72] studied the effects of seven specimens of respirable talc dust on mouse peritoneal macrophages, and observed mild, but consistent, cytotoxicity and suggested that talc could be fibrogenic. Again, there is no evidence that fibrosis plays a role in ovarian cancer pathogenesis.
- **Hamilton *et al.*** [73], on the other hand, found that talc caused a small *increase* in the proliferation of mouse bone marrow-derived macrophages (the opposite of the effects seen by Davies *et al.* on peritoneal macrophages). At higher doses, toxicity was observed, however. Based on these data, they argue that talc could cause granulomas. Indeed, granulomas were seen in the talc injection studies noted

above, but granulomas are not seen in women who have talc particles in their ovaries or as part of ovarian carcinogenesis.

*o) Effect of talc on ovarian surface epithelial cells.* Several of plaintiffs' experts (including Dr. Zelikoff) cite work by Buz'Zard and Lau [74] as evidence that talc is pro-oxidative and causes transformation of ovarian cells. This paper examined the effects of talc on immortalized human ovarian granulosa (GC1a) cells, immortalized human ovarian surface epithelial (OSE2a) cells and primary human polymorphonuclear leukocytes (PMNs; PMNs, also known as neutrophils, are the major white blood cell in human peripheral blood). The authors claimed that talc increased cell viability (cell number) of OSE2a and GC1a cells at low doses, but decreased it at higher doses (>200 ug/ml). They also claim that it increased the growth of these cell lines in soft agar at 5ug/ml and 20 ug/ml. At low doses, talc decreased ROS generation in OSE2a and increased ROS in GC1a cells, while decreasing ROS at higher talc concentrations in OSE2a cells. Finally, they find that talc causes increased ROS generation in PMNs across a broad dose range. In my opinion, this study, and its interpretation by plaintiffs' experts, is seriously flawed, for multiple reasons:

- The talc was obtained from a standard chemical reagent company, Sigma, and its quality, mineral and/or fibrous content and composition were not assessed.
- Granulosa cells are totally irrelevant to the study of epithelial ovarian carcinoma, meaning that the experiments with GC1a cells are not germane to the plaintiffs' case.
- OSE2a cells are a single, immortalized cell line, produced by transformation of normal OSE from a single woman of reproductive age with large T antigen of SV40. The use of these cells as a model for the early events of ovarian carcinogenesis is problematic on multiple levels. First, normal OSE is not the cell-of-origin for most ovarian cancer. Second, large T antigen is a viral gene product that evokes changes equivalent to at least two of the transformation events needed for ovarian carcinogenesis. Third, large T-transformed cells are genetically unstable, and no two cells transformed in this way are the same. Hence, this choice of cell system is inapt for studying mechanisms of ovarian carcinogenesis.
- Notwithstanding the choice of experimental system, the effects on proliferation are very small, quite dose-sensitive, and not likely to be biologically relevant.
- Of note, the purported pro-oncogenic effects on proliferation and ROS occur at two different doses of talc. As noted several times above, it is difficult to know what would be an appropriate dose to model the supposed level of talc in the GU tract of women exposed to perineal dusting powder.
- Growth in soft agar does not mean tumorigenicity – at least not with human cells, and as with the growth effects, at higher concentration, soft agar colony formation

is eliminated by talc treatment.

- The relevance of the PMN experiments is not clear. No role for neutrophils in ovarian carcinogenesis has been suggested by plaintiffs' experts, much less demonstrated experimentally.

- p) *Effect of talc on CA125 levels.* (p. 25) Dr. Zelikoff cites work by plaintiffs' expert Dr. Saed (discussed above) that talc induces the expression of the cancer antigen CA125 in normal ovarian cells and ovarian cancer cells. Even if these observations are true, there is no obvious relevance to ovarian cancer pathogenesis. As Dr. Zelikoff notes, CA125 is a "biomarker" for ovarian cancer detection, but it has no known role in ovarian cancer *causation*. Whether or not talc induces CA-125 expression says nothing about talc having any carcinogenic effect. Notably, in her deposition (p. 352), Zelikoff states that CA125 is MUC1. CA125 is, however, MUC16, raising the possibility that she is confusing these two proteins.
- q) *Effect of talc on expression of redox enzymes.* Dr. Zelikoff also cites "[e]merging science" (p. 25) from the Saed laboratory claiming that talc treatment of ovarian cancer cell lines and normal ovarian cells causes changes in the levels of mRNA for multiple pro-oxidant and anti-oxidant genes. The multiple problems with this work have been detailed above. Also, in her deposition (p. 236), Dr. Zelikoff states that talc leads to changes in gene expression, which "can be inferred as a mutation." This statement is categorically incorrect – changing the media on cells can cause changes in gene expression. Changing temperature can change gene expression. In no way can one "infer" a mutation merely because gene expression is altered.
- r) *Women with certain genetic variants have increased risk of ovarian cancer with talc use.* Dr. Zelikoff (p. 26) points to epidemiological data from Gates *et al.* [75] who carried out a case-control study genotyping SNPs in *GSTM1*, *GSTT1* and *NAT2* in participants from the New England based Case-Control and Nurses Health studies. The authors found that these SNPs were not themselves associated with risk, but the association of ovarian cancer with talc use was stronger in women with the GST-null genotype, and further enhanced in women with the *GST1-null* and *GSTM1-present*. The study concludes that "women with certain genetic variants may have a higher risk of ovarian cancer associated with talc use." However, the authors also specifically stated that "...additional research is needed to confirm these findings and to explore potential mechanisms for these interactions...." There appears to have been no subsequent follow up/confirmation of these data. Given that positive results are nearly always published, whereas negative results often are not (a phenomenon termed "publication bias"), it seems likely that these observations are not reproducible (or the authors would have published a subsequent paper verifying the association). Also, it should be noted that no biological/biochemical mechanism is available to explain why a higher level of *GSTM1* and a lower level of *GST1* increase interaction with talc, as these enzymes both catalyze the same biochemical reaction

Several additional lines of evidence argue against the “talc-induced inflammation model” of ovarian carcinogenesis proposed by the authors, most which have been cited above. First and foremost, whereas the evidence cited by plaintiffs’ experts is indirect, involves irrelevant cell lines, and/or is not definitive, the most direct evidence available contradicts their argument. As noted, injection of talc directly into the ovarian bursa of animals does NOT evoke inflammation, much less cancer. Similarly, women with talc particles in their ovaries do not show evidence of inflammation. Nor am I aware of any publications that have reported finding STICs, the only known pre-neoplastic lesion in HGSOV, in women or animals with talc in their genitourinary tracts. Conversely, a recent study found “no significant correlation . . . between serous carcinoma and histological signs of inflammation or chronic tubal injury” [66]. Inflammatory diseases, such as rheumatoid arthritis, systemic lupus erythematosus, psoriatic arthritis, etc., are not known risk factors for ovarian cancer [43]. And finally, there is no consistent evidence that NSAIDs mitigate ovarian cancer risk [52, 76-83].

4. **Consideration of Alternative Explanations:** As with any weak epidemiologic association, the use of talc could be associated with other conditions that promote ovarian cancer. For example, women who use talc might be more likely to have a sub-clinical infection. Also, since the publication of these epidemiology studies, numerous additional strong risk genes for ovarian cancer have been identified, as have multiple weaker risk alleles. These were not tested in the patient populations used in these studies, and thus might not have been distributed equally in the talc and non-talc groups. In the case-control studies, recall bias is a major, demonstrable concern that has not been adequately eliminated. One of the major meta-analyses [48] found significant evidence of heterogeneity, complicating the conclusions that could be drawn. Heterogeneity means that the designs of the studies have so many differences that it might not be valid to combine them.
5. **Dose-Response:** An agent that has *bona fide* pro-oncogenic effects is expected to show increasing effect with increasing dose of the agent. Yet the epidemiologic data fail to show a compelling dose-response relationship.
  - None of the cohort studies reveals a dose-response relationship [53, 84-86].
  - Multiple case-control studies also fail to show evidence of a dose-response:
    - 1) Mills *et al.* [87] found essentially no difference in the odds ratio for the lowest and highest quartiles of cumulative exposure ((1.03 (0.59-1.80)) and (1.06 (0.62-1.83)), respectively) and concluded that “no dose response association was found.”
    - 2) Cook *et al.* [88] looked for an association across various strata of “cumulative lifetime days,” and saw no statistically significant elevated risk for any of the four categories.
    - 3) Meta-analyses and pooled studies have concluded that no clear, consistent dose-response relationship can be demonstrated; e.g., [45, 47, 48, 89, 90].

- 4) The National Cancer Institute and the FDA have concluded that a dose-response relationship has not been found. (Nat'l Cancer Inst., Ovarian, Fallopian Tube, and Primary Peritoneal Cancer Prevention (PDQ®)–Health Professional Version, <https://www.cancer.gov/types/ovarian/hp/ovarian-prevention-pdq> (last updated June 22, 2018); Letter from Food & Drug Admin., Dep't of Health & Human Servs., to Samuel S. Epstein, M.D., Cancer Prevention Coalition, University of Illinois - Chicago School of Public Health (Apr. 1, 2014).) The recent Health Canada analysis noted that “concerns that the actual exposure experienced by these women over the past 40-50 years is not well understood [45].”
  - 5) Some observational studies have argued for a dose-response relationship (e.g., [49, 50, 91], but these studies and their conclusions have significant issues. It is particularly difficult to retroactively quantify exposure. Also, exposure via diaphragms or condoms is not consistently associated with risk, even though such routes might be expected to provide the highest, and certainly the most direct, exposure. As noted above, proponents of talc transit have suggested that sexual activity facilitates exposure. In that case, one would expect talc on condoms or diaphragms to be particularly dangerous.
6. **Coherence:** A theory that an agent causes disease should be internally coherent and also fit with existing, accepted science. But plaintiffs' experts' theories do not satisfy this requirement. In particular, humans given high doses of talc in other body cavities (e.g., via pleurodesis) or exposed occupationally do not have increased cancer risk. Yet most of the pro-oncogenic mechanisms proposed by plaintiffs' experts would be expected to operate in multiple body sites. Nor does it make logical sense that talc use would cause multiple subtypes of ovarian cancer, which have different cells of origin, different types of mutations and mutational effects, and therefore likely different oncogenic mechanisms.

#### IV. CONCLUSIONS AND SUMMARY OF OPINIONS

Scientific support for the theory that talc use can cause ovarian cancer is lacking. The plaintiffs' experts' causation theories do not comport with what we know about carcinogenesis generally or the development of ovarian cancer specifically; nor do they have sufficient support from epidemiological research. In particular, Dr. Saed's work is rife with errors and overstated claims that betray a lack of understanding of cancer genetics – perhaps most notably his claim that talc induces specific point mutations in certain SNPs. Moreover, Dr. Saed's work, even if the significant errors, gaps and irregularities in his lab work are ignored, rests on a series of totally unsubstantiated assumptions, including the role (if any) of inflammation or oxidant states in ovarian cancer pathogenesis, the relevance (if any) of certain SNPs to ovarian cancer, and the significance (if any) of elevated CA-125 levels to ovarian carcinogenesis. More generally, the plaintiffs' experts' theories of biological mechanism lack support in the literature – indeed, if anything, existing literature tends to negate, rather than support, their proposed mechanism. Finally, evidence from the epidemiological literature shows only weak or nonexistent associations between talcum powder use and ovarian cancer and has failed to demonstrate any strong evidence of dose-response.

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## Materials Considered

### *Expert Reports*

- 2018.11.12 - Expert Report of Michael M. Crowley, PhD
- 2018.11.14 - Expert Report of William E. Longo, PhD & Mark W. Rigler, PhD
- 2018.11.15 - Expert Report of Sarah Kane, MD
- 2018.11.16 - Expert Report of Alan Campion, PhD
- 2018.11.16 - Expert Report of Anne McTiernan, MD PhD
- 2018.11.16 - Expert Report of April Zambelli-Weiner, PhD, MPH
- 2018.11.16 - Expert Report of Arch Carson, MD, PhD
- 2018.11.16 - Expert Report of Daniel L. Clarke-Pearson, MD
- 2018.11.16 - Expert Report of David Kessler, MD
- 2018.11.16 - Expert Report of Ellen Blair Smith, MD
- 2018.11.16 - Expert Report of Ghassan Saed, PhD
- 2018.11.16 - Expert Report of Jack Siemiatycki, MSc, PhD
- 2018.11.16 - Expert Report of Judith Wolf, MD
- 2018.11.16 - Expert Report of Judith Zelikoff, PhD
- 2018.11.16 - Expert Report of Laura Plunkett, PhD, DABT
- 2018.11.16 - Expert Report of Mark Krekeler, PhD
- 2018.11.16 - Expert Report of Patricia Moorman, MSPH, PhD
- 2018.11.16 - Expert Report of Rebecca Smith-Bindman, MD
- 2018.11.16 - Expert Report of Robert B. Cook, PhD
- 2018.11.16 - Expert Report of Shawn Levy, PhD
- 2018.11.16 - Expert Report of Sonal Singh, MD, MPH
- 2019.01.15 - Supp. Expert Report of William E. Longo, PhD & Mark W. Rigler, PhD
- 2019.01.17 - Addendum to the Expert Report of Mark Krekeler, PhD
- 2019.01.22 - Amended Expert Report of Robert B. Cook, PhD

### *Deposition Transcripts*

- 2019.01.21 - Zelikoff, Judith Deposition Transcript
- 2019.01.23 - Saed, Ghassan Deposition Transcript
- 2019.02.14 - Saed, Ghassan Deposition Transcript

### *Internet Resources*

- <https://cancer.sanger.ac.uk/cosmic>
- <https://www.ebi.ac.uk/gwas/>
- <http://biorxiv.org/cgi/content/short/481200v1>
- [https://www.cdc.gov/tobacco/data\\_statistics/sgr/50th-anniversary/pdfs/fs\\_smoking\\_cancer\\_508.pdf](https://www.cdc.gov/tobacco/data_statistics/sgr/50th-anniversary/pdfs/fs_smoking_cancer_508.pdf)
- <https://portals.broadinstitute.org/ccle>
- <https://www.ebi.ac.uk/gwas/genes/MPO>
- <https://www.cancer.gov/types/ovarian/hp/ovarian-prevention-pdq>
- [https://ntp.niehs.nih.gov/ntp/roc/content/listed\\_substances\\_508.pdf](https://ntp.niehs.nih.gov/ntp/roc/content/listed_substances_508.pdf)

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*Other*

- Documents produced by Ghassan Saed
- Int'l Agency For Research On Cancer, World Health Org., *93 Monographs on the Evaluation of Carcinogenic Risks to Humans: Carbon Black, Titanium Dioxide, and Talc* (2010)
- Int'l Agency for Research on Cancer, World Health Org., *IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, No. 100C: Arsenic, Metals, Fibres, and Dusts* (2012)
- Letter from Food & Drug Admin., Dep't of Health & Human Servs., to Samuel S. Epstein, M.D., Cancer Prevention Coalition, University of Illinois - Chicago School of Public Health (Apr. 1, 2014)  
The Human Cancer Genome Atlas

# APPENDIX A

**APPENDIX A**  
**GWAS ASSOCIATIONS FOR OVARIAN CARCINOMAS**  
**(NOTE LACK OF GENES INCLUDED IN SAED'S LAB WORK)**

<b>Region</b>	<b>Reported Gene</b>	<b>Mapped Gene</b>	<b>Disease/Trait</b>	<b>Source</b>
9p22.2	NR	BNC2 - LOC105375983	Epithelial ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
3q25.31	NR	METTL15P1 - LINC00886	Epithelial ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
3q25.31	NR	METTL15P1 - LINC00886	High-grade serous ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
9p22.2	NR	BNC2 - LOC105375983	High-grade serous ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
3q25.31	NR	METTL15P1 - LINC00886	Serous invasive ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
9p22.2	NR	BNC2 - LOC105375983	Serous invasive ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
3q25.31	NR	METTL15P1 - LINC00886	Invasive epithelial ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
9p22.2	NR	BNC2 - LOC105375983	Invasive epithelial ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
10q26.13	FGFR2	FGFR2	Cancer (pleiotropy)	Fehring G. Cross-Cancer Genome-Wide Analysis of Lung, Ovary, Breast, Prostate, and Colorectal Cancer Reveals Novel Pleiotropic Associations. Cancer Res. 2016 Sep 1;76(17):5103-14.
3q25.31	NR	TIPARP	Ovarian cancer	Pharoah PD. GWAS meta-analysis and replication identifies three new susceptibility loci for ovarian cancer. Nat Genet. 2013 Apr;45(4):362-70, 370e1-2.

**APPENDIX A****GWAS ASSOCIATIONS FOR OVARIAN CARCINOMAS  
(NOTE LACK OF GENES INCLUDED IN SAED'S LAB WORK)**

<b>Region</b>	<b>Reported Gene</b>	<b>Mapped Gene</b>	<b>Disease/Trait</b>	<b>Source</b>
9p22.2	NR	BNC2 - LOC105375983	Ovarian cancer	Pharoah PD. GWAS meta-analysis and replication identifies three new susceptibility loci for ovarian cancer. Nat Genet. 2013 Apr;45(4):362-70, 370e1-2.
3q25.31	NR	TIPARP	Ovarian cancer	Pharoah PD. GWAS meta-analysis and replication identifies three new susceptibility loci for ovarian cancer. Nat Genet. 2013 Apr;45(4):362-70, 370e1-2.
9p22.2	NR	BNC2 - LOC105375983	Ovarian cancer	Pharoah PD. GWAS meta-analysis and replication identifies three new susceptibility loci for ovarian cancer. Nat Genet. 2013 Apr;45(4):362-70, 370e1-2.
17q12	HNF1B	HNF1B	Cancer (pleiotropy)	Fehringer G. Cross-Cancer Genome-Wide Analysis of Lung, Ovary, Breast, Prostate, and Colorectal Cancer Reveals Novel Pleiotropic Associations. Cancer Res. 2016 Sep 1;76(17):5103-14.
19p13.11	NR	BABA M1 - ANKLE1	High-grade serous ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
8q24.21	NR	LINC00824	Epithelial ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
8q24.21	NR	LINC00824	Serous invasive ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
19p13.11	NR	BABA M1 - ANKLE1	Serous invasive ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
8q24.21	NR	LINC00824	High-grade serous ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
5p15.33	NR	TERT	Low-grade serous and serous borderline ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.

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<b>Region</b>	<b>Reported Gene</b>	<b>Mapped Gene</b>	<b>Disease/Trait</b>	<b>Source</b>
17q21.3 1	NR	PLEKH M1	Epithelial ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
19p13.1 1	NR	BABA M1 - ANKLE 1	Epithelial ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
9p22.2	BNC2, LOC64857 0, CNTLN	BNC2 - LOC105 375983	Ovarian cancer	Song H. A genome-wide association study identifies a new ovarian cancer susceptibility locus on 9p22.2. Nat Genet. 2009 Sep;41(9):996-1000.
5p15.33	NR	TERT	Serous borderline ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
8q24.21	NR	LINC00 824	Ovarian cancer	Pharoah PD. GWAS meta-analysis and replication identifies three new susceptibility loci for ovarian cancer. Nat Genet. 2013 Apr;45(4):362-70, 370e1-2.
19p13.1 1	NR	BABA M1 - ANKLE 1	Invasive epithelial ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
17q21.3 2	NR	SKAP1	Epithelial ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
8q24.21	NR	LINC00 824	Low-grade serous and serous borderline ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
8q24.21	NR	LINC00 824	Invasive epithelial ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
12q13.1 3	KRT8	KRT8	Cancer (pleiotropy)	Fehring G. Cross-Cancer Genome-Wide Analysis of Lung, Ovary, Breast, Prostate, and Colorectal Cancer Reveals Novel Pleiotropic Associations. Cancer Res. 2016 Sep 1;76(17):5103-14.

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**GWAS ASSOCIATIONS FOR OVARIAN CARCINOMAS**  
**(NOTE LACK OF GENES INCLUDED IN SAED'S LAB WORK)**

<b>Region</b>	<b>Reported Gene</b>	<b>Mapped Gene</b>	<b>Disease/Trait</b>	<b>Source</b>
2q31.1	NR	HAGLR OS, HAGLR	Epithelial ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
2q31.1	NR	HOXD3	Epithelial ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
17q21.3 2	NR	SKAP1	Serous invasive ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
9p22.2	NR	BNC2 - LOC105 375983	Ovarian cancer in BRCA1 mutation carriers	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
2q31.1	NR	HAGLR OS, HAGLR	Serous invasive ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
19p13.1 1	NR	BABA M1	Ovarian cancer	Pharoah PD. GWAS meta-analysis and replication identifies three new susceptibility loci for ovarian cancer. Nat Genet. 2013 Apr;45(4):362-70, 370e1-2.
2q31.1	NR	HOXD3	Serous invasive ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
11q13.3	Intergenic	LOC105 369366 - LOC105 369367	Cancer (pleiotropy)	Fehring G. Cross-Cancer Genome-Wide Analysis of Lung, Ovary, Breast, Prostate, and Colorectal Cancer Reveals Novel Pleiotropic Associations. Cancer Res. 2016 Sep 1;76(17):5103-14.
2q31.1	NR	HOXD3	Invasive epithelial ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
2q31.1	NR	HAGLR OS, HAGLR	Invasive epithelial ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.

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<b>Region</b>	<b>Reported Gene</b>	<b>Mapped Gene</b>	<b>Disease/Trait</b>	<b>Source</b>
2q31.1	HOXD1, HOXD3	HAGLR	Ovarian cancer	Goode EL. A genome-wide association study identifies susceptibility loci for ovarian cancer at 2q31 and 8q24. Nat Genet. 2010 Oct;42(10):874-9.
17q21.3 2	NR	SKAP1	High-grade serous ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
17q21.3 1	NR	PLEKH M1	Invasive epithelial ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
17q21.3 1	NR	PLEKH M1	High-grade serous ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
2q31.1	NR	HAGLR OS, HAGLR	High-grade serous ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
17q23.2	BRIP1	BRIP1	Ovarian cancer	Rafnar T. Mutations in BRIP1 confer high risk of ovarian cancer. Nat Genet. 2011 Oct 2;43(11):1104-7.
2q31.1	NR	HOXD3	High-grade serous ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
17q21.3 2	NR	SKAP1	Invasive epithelial ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
5p15.33	NR	TERT	Serous invasive ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
8q24.21	NR	LINC00824	Serous borderline ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
8q24.21	MYC	LINC00824	Ovarian cancer	Pharoah PD. GWAS meta-analysis and replication identifies three new susceptibility loci for ovarian cancer. Nat Genet. 2013 Apr;45(4):362-70, 370e1-2.

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<b>Region</b>	<b>Reported Gene</b>	<b>Mapped Gene</b>	<b>Disease/Trait</b>	<b>Source</b>
17q21.31	NR	PLEKH M1	Serous invasive ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
5q11.2	Intergenic	LOC101928448 - LOC105378979	Cancer (pleiotropy)	Fehring G. Cross-Cancer Genome-Wide Analysis of Lung, Ovary, Breast, Prostate, and Colorectal Cancer Reveals Novel Pleiotropic Associations. Cancer Res. 2016 Sep 1;76(17):5103-14.
5p15.33	NR	TERT	High-grade serous ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
*	NR	*	High-grade serous ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
13q13.1	BRCA2	BRCA2	Cancer	Fehring G. Cross-Cancer Genome-Wide Analysis of Lung, Ovary, Breast, Prostate, and Colorectal Cancer Reveals Novel Pleiotropic Associations. Cancer Res. 2016 Sep 1;76(17):5103-14.
*	NR	*	Epithelial ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
10p12.31	NR	MLLT10	Epithelial ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
2q31.1	NR	HAGLR	Ovarian cancer	Pharoah PD. GWAS meta-analysis and replication identifies three new susceptibility loci for ovarian cancer. Nat Genet. 2013 Apr;45(4):362-70, 370e1-2.
9p22.2	cHMP4C, FABP5, PMP2, FABP12, IMPA1, SLC10A5, ZFAND1, SNX16, FABP4	BNC2 - LOC105375983	Ovarian cancer in BRCA1 mutation carriers	Couch FJ. Genome-wide association study in BRCA1 mutation carriers identifies novel loci associated with breast and ovarian cancer risk. PLoS Genet. 2013;9(3):e1003212.

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<b>Region</b>	<b>Reported Gene</b>	<b>Mapped Gene</b>	<b>Disease/Trait</b>	<b>Source</b>
*	NR	*	Serous invasive ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
9p22.2	NR	BNC2 - LOC105375983	Ovarian cancer in BRCA2 mutation carriers	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
4q24	Intergenic	LOC100288146 - TET2	Cancer (pleiotropy)	Fehringer G. Cross-Cancer Genome-Wide Analysis of Lung, Ovary, Breast, Prostate, and Colorectal Cancer Reveals Novel Pleiotropic Associations. Cancer Res. 2016 Sep 1;76(17):5103-14.
5p15.33	TERT	TERT	Cancer (pleiotropy)	Fehringer G. Cross-Cancer Genome-Wide Analysis of Lung, Ovary, Breast, Prostate, and Colorectal Cancer Reveals Novel Pleiotropic Associations. Cancer Res. 2016 Sep 1;76(17):5103-14.
17q12	NR	HNF1B	Serous invasive ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
17q12	NR	HNF1B	Epithelial ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
14q24.1	RAD51B	RAD51B	Cancer (pleiotropy)	Fehringer G. Cross-Cancer Genome-Wide Analysis of Lung, Ovary, Breast, Prostate, and Colorectal Cancer Reveals Novel Pleiotropic Associations. Cancer Res. 2016 Sep 1;76(17):5103-14.
2q31.1	NR	HAGLR	Ovarian cancer	Pharoah PD. GWAS meta-analysis and replication identifies three new susceptibility loci for ovarian cancer. Nat Genet. 2013 Apr;45(4):362-70, 370e1-2.
17q21.32	NR	SKAP1	Ovarian cancer	Pharoah PD. GWAS meta-analysis and replication identifies three new susceptibility loci for ovarian cancer. Nat Genet. 2013 Apr;45(4):362-70, 370e1-2.

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<b>Region</b>	<b>Reported Gene</b>	<b>Mapped Gene</b>	<b>Disease/Trait</b>	<b>Source</b>
*	NR	*	Epithelial ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
1p36.33	Intergenic	DVL1 - MXRA8	Cancer (pleiotropy)	Fehringer G. Cross-Cancer Genome-Wide Analysis of Lung, Ovary, Breast, Prostate, and Colorectal Cancer Reveals Novel Pleiotropic Associations. Cancer Res. 2016 Sep 1;76(17):5103-14.
13q13.1	BRCA2	BRCA2	Cancer (pleiotropy)	Fehringer G. Cross-Cancer Genome-Wide Analysis of Lung, Ovary, Breast, Prostate, and Colorectal Cancer Reveals Novel Pleiotropic Associations. Cancer Res. 2016 Sep 1;76(17):5103-14.
12q24.31	NR	RPL12P33 - HNF1A-AS1	Epithelial ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
5p15.33	NR	TERT	Serous invasive ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
8q21.13	CHMP4C, FABP5, PMP2, FABP12, IMPA1, SLC10A5, ZFAND1, SNX16, FABP4	CHMP4C	Ovarian cancer	Pharoah PD. GWAS meta-analysis and replication identifies three new susceptibility loci for ovarian cancer. Nat Genet. 2013 Apr;45(4):362-70, 370e1-2.
5p15.33	NR	TERT	Invasive epithelial ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.

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<b>Region</b>	<b>Reported Gene</b>	<b>Mapped Gene</b>	<b>Disease/Trait</b>	<b>Source</b>
17q12	HNF1B, ACACA, C17orf78, TADA2A, DUSP14, SYNRG, DDX52, TBC1D3F, TBC1D3, MRPL45, GPR179, SOCS7, ARHGAP23	HNF1B	Ovarian cancer	Pharoah PD. GWAS meta-analysis and replication identifies three new susceptibility loci for ovarian cancer. Nat Genet. 2013 Apr;45(4):362-70, 370e1-2.
*	NR	*	Invasive epithelial ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
10p12.31	NR	MLLT10	Invasive epithelial ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
*	NR	*	High-grade serous ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
17q12	HNF1B	HNF1B	Cancer	Fehring G. Cross-Cancer Genome-Wide Analysis of Lung, Ovary, Breast, Prostate, and Colorectal Cancer Reveals Novel Pleiotropic Associations. Cancer Res. 2016 Sep 1;76(17):5103-14.
5p15.33	NR	TERT	Low-grade serous and serous borderline ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
1p34.3	NR	RSPO1	Epithelial ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.

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<b>Region</b>	<b>Reported Gene</b>	<b>Mapped Gene</b>	<b>Disease/Trait</b>	<b>Source</b>
3p24.1	NEK10	NEK10	Cancer (pleiotropy)	Fehring G. Cross-Cancer Genome-Wide Analysis of Lung, Ovary, Breast, Prostate, and Colorectal Cancer Reveals Novel Pleiotropic Associations. Cancer Res. 2016 Sep 1;76(17):5103-14.
19p13.11	BABAM1	BABAM1 - ANKLE1	Cancer (pleiotropy)	Fehring G. Cross-Cancer Genome-Wide Analysis of Lung, Ovary, Breast, Prostate, and Colorectal Cancer Reveals Novel Pleiotropic Associations. Cancer Res. 2016 Sep 1;76(17):5103-14.
*	NR	*	Serous invasive ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
8q21.13	NR	LINC01111	Low-grade serous and serous borderline ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
8q24.21	NR	PVT1	Epithelial ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
20q11.22	Intergenic	RPS2P1 - ASIP	Cancer	Fehring G. Cross-Cancer Genome-Wide Analysis of Lung, Ovary, Breast, Prostate, and Colorectal Cancer Reveals Novel Pleiotropic Associations. Cancer Res. 2016 Sep 1;76(17):5103-14.
8q24.21	MYC, THEM75	LINC00824	Ovarian cancer	Goode EL. A genome-wide association study identifies susceptibility loci for ovarian cancer at 2q31 and 8q24. Nat Genet. 2010 Oct;42(10):874-9.
17q12	NR	HNF1B	High-grade serous ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
13q13.1	FRY	FRY	Cancer (pleiotropy)	Fehring G. Cross-Cancer Genome-Wide Analysis of Lung, Ovary, Breast, Prostate, and Colorectal Cancer Reveals Novel Pleiotropic Associations. Cancer Res. 2016 Sep 1;76(17):5103-14.

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<b>Region</b>	<b>Reported Gene</b>	<b>Mapped Gene</b>	<b>Disease/Trait</b>	<b>Source</b>
5p15.33	NR	TERT	Serous borderline ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
22q12.1	NR	TTC28, LOC101929594	Serous invasive ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
17q21.32	NR	SKAP1	Ovarian cancer	Pharoah PD. GWAS meta-analysis and replication identifies three new susceptibility loci for ovarian cancer. Nat Genet. 2013 Apr;45(4):362-70, 370e1-2.
8q21.13	CHMP4C, FABP5, PMP2, FABP12, IMPA1, SLC10A5, ZFAND1, SNX16, FABP4	CHMP4C	Ovarian cancer	Pharoah PD. GWAS meta-analysis and replication identifies three new susceptibility loci for ovarian cancer. Nat Genet. 2013 Apr;45(4):362-70, 370e1-2.
17q12	NR	HNF1B	Ovarian clear cell cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
10p12.31	NR	MLLT10	Serous invasive ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
17q12	NR	HNF1B	Epithelial ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
17q21.31	intergenic	PLEKH M1	Ovarian cancer in BRCA1 mutation carriers	Couch FJ. Genome-wide association study in BRCA1 mutation carriers identifies novel loci associated with breast and ovarian cancer risk. PLoS Genet. 2013;9(3):e1003212.
17q21.31	NR	PLEKH M1	Ovarian cancer in BRCA1 mutation carriers	Couch FJ. Genome-wide association study in BRCA1 mutation carriers identifies novel loci associated with breast and ovarian cancer risk. PLoS Genet. 2013;9(3):e1003212.

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<b>Region</b>	<b>Reported Gene</b>	<b>Mapped Gene</b>	<b>Disease/Trait</b>	<b>Source</b>
17q12	NR	HNF1B	Serous invasive ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.
22q12.1	NR	TTC28, LOC101929594	High-grade serous ovarian cancer	Phelan CM. Identification of 12 new susceptibility loci for different histotypes of epithelial ovarian cancer. Nat Genet. 2017 May;49(5):680-691.

\* In some instances, no region or mapped gene is identified for a given SNP. Most likely, these are in regulatory regions that undergo looping to the gene of interest, but the looping has not been defined yet.

# **APPENDIX B**

22 February 2019

## CURRICULUM VITAE

**Name:** Benjamin G. Neel

**Office Address:** Laura and Isaac Perlmutter Cancer Center  
522 First Avenue  
Smilow Building 12th Floor, Suite 1201  
New York, NY 10016  
Tel: 212.263.3019, Fax: 212.263.9190  
benjamin.neel@nyulangone.org

### Education:

05/1977 A.B. Cornell University College of Arts and Sciences, Ithaca, NY  
06/1982 Ph.D. Rockefeller University, New York, NY  
06/1983 M.D. Cornell University Medical College, New York, NY

### Postdoctoral Training:

#### Internship and Residencies:

1983-1985 Medical Resident, Beth Israel Hospital, Boston, MA  
1985-1987 Special Resident, Beth Israel Hospital, Boston, MA

#### Research Fellowships:

1985-1989 Special Fellow, Leukemia Society of America (Molecular Biology), Harvard University Department of Cell and Developmental Biology, Cambridge, MA  
1987-1988 Postdoctoral Fellow, Harvard University Department of Cell and Developmental Biology, Cambridge, MA

### Academic Appointment:

1988-1993 Assistant Professor of Medicine, Harvard Medical School, Boston, MA  
1993-1999 Associate Professor of Medicine, Harvard Medical School, Boston, MA  
1999-2007 Professor of Medicine, Harvard Medical School, Boston, MA  
2006 -2007 William B. Castle Professor of Medicine, Harvard Medical School, Boston, MA  
2007 -2015 Professor of Medical Biophysics, University of Toronto, Toronto, ON  
2007 - 2015 Canada Research Chair, Tier 1  
2015- Professor of Medicine, NYU Langone Health, School of Medicine, New York, NY

### Hospital Appointment:

1994-2007 Director, Cancer Biology Program, Beth Israel Deaconess Medical Center  
2003-2007 Deputy Director, Basic Research, Hematology/Oncology Division, Beth Israel Deaconess Medical Center, Boston, MA  
2007- 2014 Director, Research, Princess Margaret Hospital Cancer Center, Toronto, ON  
2008- 2014 Founding Director, The Campbell Family Institute for Cancer Research  
2015- Laura and Isaac Perlmutter Cancer Center Director, NYU Langone Health, School of Medicine, New York, NY

### Others:

2015- SiriusXM, Co-Host, Doctor Radio Oncology Special

**Licensure and Certification:**

1987 Diplomat, American Board of Internal Medicine  
1984 Massachusetts License (inactive)

**Awards and Honors:**

1976 Phi Beta Kappa  
1977 Phi Kappa Phi  
1983 Associated Medical Schools of New York, Award for Biomedical Research  
1985 Special Fellowship, Leukemia Society of America  
1990 Harvard University Nominee for Pew Scholars Program  
1992 Harvard University/Hoffman-LaRoche Institute for Chemistry and Medicine  
Grant Recipient  
1992 American Cancer Society, Junior Faculty Research Award  
1992 American Association for Cancer Research, Gertrude Elion Award  
2003, 2008 NIH MERIT Award (Renewed)  
2007- Canada Research Chair, Tier 1  
2009- Premier of Ontario Summit Award  
2012- 2015 AACR Board of Directors, Elected  
2015- Association of American Physicians, Elected Member

**Selected Invited Talks:**

1996 EMBO Workshop on Protein Dephosphorylation, Switzerland  
1996 British Society of Cell Biology Joint Spring Meeting, U.K.  
1996 Hanson Symposium on Molecular Mechanisms of Oncogenesis,  
Adelaide, Australia  
1997 Keystone Meeting on Cell Signaling, Colorado  
1997 FASEB Summer Research Conference on Hematopoietic  
Neoplasms, Vermont  
1997 EMBO-FEBS Workshop on Protein Phosphatases and Protein  
Dephosphorylation, Oxford, England  
1997 Tokyo International Symposium, Tokyo, Japan  
1998 Keystone Meeting on JAK/STAT Signalling, Colorado  
1998 Gordon Research Conference on Second Messengers and  
Protein Phosphorylation, New Hampshire  
1998 FASEB Summer Research Conference on Protein Phosphatases,  
Copper Mountain, Colorado  
1998 International Hematology Congress, Amsterdam  
1998 University of Toronto Department of Immunology Eaton Lectureship  
1999 First Harvard/Munich AML Workshop, Munich, Germany  
1999 FASEB Meeting on Biology of ImmunoReceptors, Saxtons River, Vermont  
2000 Lorne Cancer Conference, Lorne, Australia  
2000 FASEB Meeting on Signal Transduction in the Immune System, Saxtons  
River, Vermont  
2000 The Second International Conference on Signal Transduction, Dubrovnik,  
Croatia  
2001 FASEB Meeting on Receptors and Signal Transduction, Cooper Mountain,  
Colorado  
2001 American Heart Association Annual Meeting, Washington, DC  
2002 Experimental Biology 2002, New Orleans, Louisiana

2002 Keystone Symposium on Molecular and Cellular Biology of Leukocyte Receptors, Lake Tahoe, California

2002 Fifth International Conference on Phosphatases and Cellular Regulation, Okazaki, Japan

2003 Europhosphatases 2003, Barcelona, Spain

2003 Gordon Conference on Cell Proliferation, New London, New Hampshire

2003 FASEB Summer Research Conference on Signal Transduction in the Immune System, Snowmass Village, Colorado

2004 12th International Conference on Second Messengers and Phosphoproteins, Montreal, Quebec, Canada

2004 FASEB Summer Research Conference on Protein Phosphatases, Snowmass Village, Colorado

2005 AACR Annual Meeting, Anaheim, California, Meet the Experts

2005 Keynote Speaker, National Neurofibromatosis International Consortium for the Molecular Biology of NF1 and NF2, Aspen, Colorado

2005 17th Pezcoller Symposium on Molecular Understanding of Solid Tumors, Trento, Italy

2005 Europhosphatases 2005, Cambridge, England

2005 FASEB Summer Research Conference on Hematological Malignancies, Saxton's River, Vermont

2005 FASEB Summer Research Conference on Growth Factor Receptor Tyrosine Kinases in Mitogenesis, Morphogenesis and Tumorigenesis Tucson, Arizona

2005 Salk/EMBL Oncogenes and Growth Control Meeting, La Jolla, California

2006 International Symposium of Kobe University on Signal Transduction, Kobe, Japan

2007 USA-Japan Cooperative Cancer Workshop on Animal Models of Hematological Malignancies, Kauai, Hawaii

2007 5<sup>th</sup> International Aachen Symposium on Cytokine Signaling, Aachen, Germany

2007 AACR Annual Meeting, Los Angeles, California, Meet the Expert

2007 Signaling and Metabolic Pathways in Cancer Workshop, Madrid, Spain

2007 FASEB Summer Research Conference on Growth Factor Receptor Tyrosine Kinases in Mitogenesis, Morphogenesis and Tumorigenesis, Tucson, Arizona

2008 20<sup>th</sup> Lorne Cancer Conference, Lorne, Australia

2008 FASEB Summer Research Conference on Protein Phosphatase Snowmass Village, Colorado

2008 Gordon Research Conference on Growth Factors and Signalling, Oxford, United Kingdom

2011 AACR Annual Meeting, Forum on Cancer Stem Cells, Moderator and Speaker

2011 Avery Steelman Lecture, University of North Carolina, Department of Pharmacology.

2012 Satellite Conference on Protein Phosphatases, Melbourne, Australia

2012 Lorne Proteomics Conference, Lorne, Australia

2012 Lorne Cancer Conference, Lorne, Australia

2012 Pathways Symposium, Koch Institute, MIT, Cambridge, MA

2012 Keynote speaker 2013 Japanese Phosphatase Meeting, Tokyo Japan

2013 Invited Speaker, AACR Conference on Synthetic Lethality, Seattle, WA

2013	Arnold S. Greenberg Lecture, U. Winnepeg
2014	Invited Speaker, Europhosphatase Meeting, Rehovot, Israel
2013	Keynote Speaker, International Conference on Systems Biology, Copenhagen, Denmark
2014	Session Chair and Invited Speaker, Current Topics in Ovarian Cancer, AACR Annual Meeting, San Diego, CA.
2014	Christie Gordon Lecture, University of Birmingham, Birmingham UK
2014	Invited Speaker, FASEB phosphatases Meeting, Nassau, Bahamas
2014	Invited Speaker, Salk Meeting on Cell Signaling, La Jolla, CA
2014	Invited Speaker, Max Planck Institute Student Symposium, Dortmund, Germany
2014	Invited Speaker, Japanese Phosphatase Society Meeting
2015	Keystone Speaker, the Biological Code of Cell Signaling - A Tribute to Tony Pawson, Steamboat Springs, Colorado
2015	Invited Speaker, Department of Oncological Sciences at Mount Sinai, New York, New York
2015	Invited Speaker, Current Topics in Cancer Therapy, AACR Annual Meeting, Philadelphia, PA
2015	Invited Speaker, Cell Signalling and its Therapeutic Implications (CSTI) Symposium, Melbourne, Australia
2015	Invited Speaker, Monash University, Melbourne, Australia
2015	Invited Speaker, Uppsala University, Uppsala, Sweden
2015	Invited Speaker, EMBO Conference Europhosphatase Meeting, Turku, Finland
2015	Invited Speaker, FASEB Protein Kinases and Protein Phosphorylation Meeting, Itasca, Illinois
2015	Oncology Grand Rounds Speaker, Georgetown-Lombardi Comprehensive Cancer Center, Washington, District of Columbia
2016	Pharmacology Seminar Course Speaker, Precision Medicine and Pharmacology at UCSD University of California, San Diego, La Jolla, California
2016	Regulatory Networks in Health and Disease Seminar Series Speaker, Department of Pharmacology and Cancer Biology at Duke Cancer Institute at Duke University School of Medicine, Durham, North Carolina
2016	Invited Speaker, 213 <sup>th</sup> Interurban Clinical Club, New York, New York
2016	Invited Speaker, Hinterzartner Kreis on Cancer Research, Lake Como, Italy
2016	Guest Speaker, 81st Cold Spring Harbor Laboratory Symposium on Quantitative Biology, Cold Spring Harbor, NY
2016	Invited Speaker, FASEB Science Research Conference on Cell Signaling in Cancer: From Mechanisms to Therapy, Snowmass, Colorado
2016	Invited Speaker, Lurie Comprehensive Cancer Center of Northwestern University, Hematology/Oncology, Grand Rounds, Chicago, Illinois
2016	Invited Speaker, Biochemical Society meeting on Phosphatases and Signalling in Health and Disease, University of Bath, Claverton Down, Bath
2016	Invited Speaker, FASEB Science Research Conference on Protein Phosphatases, Steamboat Springs, Colorado
2016	Invited Speaker, Post-Translational Regulation of Cell Signaling Meeting, Salk Institute, La Jolla, California
2016	Invited Speaker, Oncology Seminar Series, Lilly NY Research, New York, New York

- 2016 Invited Speaker, Animal models for hematopoietic malignancies, Nice, France
- 2016 Guest Speaker, 12<sup>th</sup> International Conference on Protein Phosphates, Kinki University, Osaka, Japan
- 2016 Seminar Speaker, Cold Spring Harbor Laboratory Seminar Series, Cold Spring Harbor, NY
- 2016 Visiting Lecturer, Frontiers in Oncology Lecture, Icahn School of Medicine at Mount Sinai Hospital, New York, New York
- 2016 Invited Speaker, Tisch Cancer Institute Grand Rounds Lecture, Icahn School of Medicine at Mount Sinai Hospital, New York, NY
- 2017 Dana-Farber Cancer Institute, Louise & Herbert Shivek, Oncology Lecture Series, Boston, MA
- 2017 UCSF Helen Diller Family Comprehensive Cancer Center, Seminar Series, San Francisco, CA
- 2017 Invited Speaker, University of Turku, Frontiers of Science Seminars, Turku, Finland
- 2017 Invited Speaker, Charite University Medical Center, Sharing Radically Novel Visions in Cancer Conference, Berlin Germany
- 2017 Invited Speaker, Meyer Cancer Center at Weill Cornell Medicine, Seminar Series, New York, NY
- 2017 Invited Speaker, EMBO Europhosphatase, Paris, France
- 2017 Invited Speaker, FASEB - Protein Kinases and Protein Phosphorylation, Cambridge, UK.
- 2017 Invited Speaker, New York Genome Center, New York, NY
- 2017 Invited Speaker, Cold Spring Harbor Asia Conference on Cell Signaling & Metabolism in Metabolism in Development & Disease, Suzhou, China.
- 2018 Invited Speaker, World Congress on Cancer, Jaipur, India.
- 2018 Invited Speaker, University of Texas MD Anderson Cancer Center, Blaffer Lecture Series, Houston, TX.
- 2018 Invited Speaker, European Association for Cancer Research, LIF AS WE KNOW IT Conference, Barcelona, Spain.
- 2018 Invited Speaker, FASEB -Cell Signaling in Cancer: from Mechanisms to Therapy, Steamboat Springs, Colorado
- 2018 Distinguished Lectureship, Albert Einstein Cancer Center, New York, NY.
- 2018 Invited Speaker, Salk Post-translational Regulation of Cell Signaling, La Jolla, CA.
- 2018 Distinguished Lectureship, University of Cincinnati College of Medicine, Cincinnati, OH.
- 2018 Invite Speaker, International Phosphatase Conference, Tokyo, Japan
- 2018 Invited Speaker, Science China Life Science Conferences on Cell Signaling, Hangzhou and Wuhan, China
- 2018 Invited Speaker, Rhode Island Hospital's Department of Hematology and Oncology Research, Scientific Meeting.

### Meetings Organized:

1995, 1997	Co-Organizer, Cold Spring Harbor Laboratory Meeting on Tyrosine
1999, 2001	Phosphorylation and Cell Signaling, New York
2003, 2005	
2007, 2009	
1999	Vice-Chair (elected), Gordon Conference on Cell Proliferation
2000	Vice-Chair (elected), FASEB Phosphatase Meeting
2001	Chair (elected), Gordon Conference on Cell Proliferation
2002	Chair (elected), FASEB Phosphatase Meeting
2011	Chair, 2012 AACR Annual Meeting Program Committee
2014	Co-organizer, Cold Spring Harbor Laboratory Meeting on Mechanisms and Models of Cancer
2015	Co-Chair, AACR Ovarian Cancer Conference, Orlando, Florida
2015	Co-Chair, WIN Symposium 2016, Paris, France

### Editorial Boards:

1993-	Editorial Board Member, Virology
1995-2000	Editorial Board Member, Journal of Biological Chemistry
1997-	Editorial Board Member, Cell Growth and Differentiation
1997-2000	Editorial Board Member, Genes and Development
1996-2000	Editorial Board Member, Molecular and Cellular Biology
2000-2010	Editor, Molecular and Cellular Biology
2002-	Editorial Board Member, Cancer Cell
2009-	Editorial Board Member, Current Opinion in Genetics and Development
2010-	Editorial Board Member, Journal of Experimental Medicine
2010-	2014 Board of Reviewing Editors, Science Signaling
2011-	Editorial Board Member, AACR, Cancer Discovery
2013-	Editorial Board Member, Journal of Clinical Investigation
2014-	Editorial Board Member, Molecular Cell

### Board Members:

2015- 2016	Centre for Commercialization of Antibodies and Biologics (CCAB), Board and Chair
2010-2016	Kolltan, Scientific Advisory Board
2014-2018	Northern Biologics, Member, Board of Directors
2014-	Northern Biologics, Co-founder and Scientific Advisory Board
2014-	Gerstner School, Memorial Sloan Kettering, External Advisory Committee
2015-	Ronald McDonald House of New York, Board of Directors
2016-	Lurie Comprehensive Cancer Center of Northwestern University, External Advisor Board
2016-	AACR Regional Advisory Subcommittee on Canada
2017-	Rutgers Cancer Institute of New Jersey, External Advisory Board
2017-	Co-Founder and Chair, Scientific Advisory Board, Navire Pharmaceuticals
2017-	Quantigic Genomics LLC, Scientific Advisory Board
2017-	Herbert Irving Comprehensive Cancer Center, at Columbia University Medical, External Scientific Advisory Board
2018-	AACI Board of Directors

2018- Max F. Perutz Laboratories, Scientific Advisory Board

**Memberships and Professional Societies:**

American Society for Microbiology (ASM)  
American Association for Cancer Research (AACR)  
American Association of Arts and Sciences (AAAS)  
American Society of Hematology (ASH)  
Affiliate Member of the New York Genome Center

**Study Sections:**

1992 Ad Hoc Reviewer for NIH DSR IRG Study Section  
1993, 1994 Study Section member, California State Tobacco Related Diseases Program  
1995 Ad Hoc Reviewer, Veterans Administration  
1995 Ad Hoc Reviewer, Israeli National Science Foundation  
1996 Reviewer for NCI-Frederick Intramural Program  
1995-1998 Member, NIH Biology II Study Section  
1997-2001 Study Section member, American Cancer Society, Mass. Division  
1998-2000 Member, NIH Molecular Biology Study Section (CDF-1)  
1997-2007 Study Section member, The Medical Foundation, Boston, MA  
2004 Member, Hematology Study Section  
2004 Reviewer, California State Breast Cancer Research Program  
2007-2010 Reviewer, STARR Cancer Consortium  
2008-2011 Study Section Member, Molecular and Integrative Signal Transduction (MIST)  
2010-2015 Member, Gairdner Award Medical Advisory Board (Selection Committee)  
2016 Ad Hoc Reviewer, Winship Cancer Center of Emory University  
2016 Reviewer, Howard Hughes Medical Institute, Investigator Review  
2016-2018 Member, AACR Award for Lifetime Achievement in Cancer Research  
Selection Committee  
2018 Chairperson, AACR Award for Lifetime Achievement in Cancer Research  
Selection Committee

**Major Research Interests:**

Tyrosine phosphatases, scaffolding adapters, signal transduction, mouse models of signaling abnormalities and human disease, breast carcinogenesis, leukemogenesis, functional genomic screening, ovarian cancer.

**Teaching Experience:**

1990-1993 Co-director, Cellular and Developmental Biology 200B: core cell biology course in Cell Biology, Division of Medical Sciences, Harvard University  
1993 Lecturer, Immunology 212 and Genetics 205  
1994 Lecturer, Core Cell Biology Course (CDB200B)  
1995-2006 Section Leader, Core Cell Biology Course (CDB200B)  
2004-2006 Co-Director, Cell Biology and Biochemistry core course, Harvard Medical School  
2004-2006 Co-Director, CB201 (Core graduate student Cell Biology Course)  
2013-2014 Lecturer, Signaling in Biochemistry - (BCH426) - Phosphatases  
2013-2014 Lecturer, Medical Biophysics Lecture – (MBP1007) - RTK signaling

## Patents:

Methods for identifying a tyrosine phosphatase abnormality associated with neoplastic disease.

Inventors: Freeman, Jr.; Robert M. (Boston, MA); Plutzky; Jorge (Boston, MA); Neel; Benjamin G. (Wayland, MA); Rosenberg; Robert D. (Brookline, MA) 5,536,636 - July 16<sup>th</sup>, 1996

Peptide which binds SH.sub.2 domains of protein tyrosine phosphatase SH-PTP1.

Inventors: Klingmuller; Ursula (Arlington, MA); Michnick; Stephen (Westmount, CA); Neel; Benjamin G. (Wayland, MA); Lorenz; Ulrike (Boston, MA); Lodish; Harvey F. (Brookline, MA) 5,659,012 - August 9<sup>th</sup>, 1997

Activated mutants of SH2-domain-containing protein tyrosine phosphatases and methods of use thereof.

Inventors: Neel, Benjamin G (Wayland, MA).; O'Reilly, Alana M. (Watertown, MA); Shoelson, Steven (Natick, MA); Pluskey, Scott (Allston, MA) 6,156,551 - Dec. 5<sup>th</sup>, 2000

Gab2(p97) gene and methods of use thereof .

Inventors: Gu, Haihua, Neel Benjamin G, Kinet, Jean-Pierre. US 2004/0086893 A1 - May 6<sup>th</sup>, 2004

Combination of mtor inhibitor and a tyrosine kinase inhibitor for the treatment of neoplasms.

Inventors: Neel, Benjamin G. and Mohi, Golam. US 2006/0094674 A1 – May 4<sup>th</sup>, 2006

Diagnosis and Treatment of Noonan Syndrome and Neoplastic Disorders.

Inventors: Neel, Benjamin G, Roberts, Amy, Kucherlapati, Raju, Araki, Toshiyuki, Swanson, KD. US 2010/0227778 A1 - September 9<sup>th</sup>, 2010

Hedgehog Pathway Inhibition for Cartilage Tumor and Metachondromatosis Treatment.

Inventors: Wentian Yang; Benjamin G. Neel. US 9,833,446 B2 – December 5, 2017

## Bibliography:

1. Anderson SM, Hayward WS, **Neel BG**, Hanafusa H. Avian erythroblastosis virus produces two messenger RNAs. **J. Virol.**, 1980; 36:676-683. PMID:PMC353695
2. Hayward WS, **Neel BG**, Astrin SM. Induction of lymphoid leukosis by avian leukosis virus: activation of a cellular onc gene by promoter insertion. **J. Supramol. Struct. Cell. Biochem.** (suppl. 5), 1981; 0:101.
3. Hayward WS, **Neel BG**, Fang J, Robinson HL, Astrin SM. Avian lymphoid leukosis is correlated with the appearance of discrete new RNAs containing viral and cellular genetic information. **Hematol Blood Transfus.** 1981;26:439-44.
4. **Neel BG**, Hayward WS, Robinson HS, Fang J, Astrin SM. Avian leukosis virus-induced tumors have common proviral integration sites and synthesize discrete new RNAs: oncogenesis by promoter insertion. **Cell** 1981 Feb;23(2):323-34. PMID 6258798

5. Hayward WS, **Neel BG**, Astrin SM. Activation of a cellular onc gene by promoter insertion in avian leukosis virus-induced lymphoid leukosis. **Nature** 1981 Apr 9;290(5806):475-80. PMID 6261142
6. **Neel BG**, Wang LH, Mathey-Prevot B, Hanafusa T, Hanafusa H, Hayward WS. Isolation of 16L virus: a rapidly transforming sarcoma virus from an avian leukosis virus induced sarcoma. **Proc. Natl. Acad. Sci. USA**, 1982 Aug;79(16):5088-92. PMCID:PMC346833
7. **Neel BG**, Gasic GP, Rogler CE, Skalka AM, Ju G, Hisinuma F, Pappas T, Astrin SM, Hayward WS. Molecular analysis of the c-myc locus in normal tissue and in avian leukosis virus-induced lymphomas. **J. Virol.**, 1982; 44:158-166. PMCID:PMC256249
8. **Neel BG**, Jhanwar SC, Chaganti RS, Hayward WS. Two human c-onc genes are located on the long arm of chromosome 8. **Proc Natl Acad Sci USA** 1982 Dec;79(24):7842-6 PMCID:PMC347445
9. Hayward WS, **Neel BG**, Shin CK, Jhanwar Sc, Chaganti, RS. The role of host c-onc genes in viral and non-viral neoplasia. **Prog Clin Biol Res.** 1983;119:119-32
10. Jhanwar SC, **Neel BG**, Hayward WS, Chaganti RSK. Localization of c-ras oncogene family on human germ-line chromosomes. **Proc. Natl. Acad. Sci. USA**, 1983 Aug;80(15):4794-7. PMCID:PMC384131
11. Jhanwar SC, **Neel BG**, Hayward WS, Chaganti RSK. Localization of the cellular oncogenes ABL, SIS and FES on human germ-like chromosomes. **Cytogenet. Cell Genet.**, 1984;38:73-5.
12. Chernoff J, Schievella AR, Jost CA, Erickson RL, **Neel BG**. Cloning of a cDNA for a major human protein-tyrosine-phosphatase. **Proc. Natl. Acad. Sci. USA**, 1990 Apr;87(7):2735-9. PMCID:PMC53765
13. Gebert JF, Moghal N, Frangioni JV, Sugarbaker DJ, **Neel BG**. High frequency of retinoic acid receptor abnormalities in human lung cancer. **Oncogene** 1991 Oct;6(10):1859-68
14. Plutzky J, **Neel BG**, Rosenberg, RD. Isolation of a src homology 2-containing tyrosine phosphatase. **Proc Natl Acad Sci U.S.A.** 1992 Feb;89(3):1123-7. PMCID: PMC48398
15. Frangioni JV, Beahm PH, Shifrin V, Jost CA, **Neel BG**. The non-transmembrane tyrosine phosphatase PTP-1B localizes to the endoplasmic reticulum via its 35 amino acid C-terminal sequence. **Cell**, 1992 Feb 7;68(3):545-60. PMID 1739967
16. Plutzky J, **Neel BG**, Rosenberg RD, Eddy RL, Shows TB. Chromosomal localization of an SH-2 containing tyrosine phosphatase. **Genomics.** 1992 Jul;13(3):869-72.
17. Shou C, Farnsworth CL, **Neel BG**, Feig LA. Molecular cloning of cDNAs encoding a guanine-nucleotide-releasing factor for RAS p21. **Nature.** 1992 Jul 23;358(6384):351-4.
18. Simmons DL, **Neel BG**, Stevens R, Evett G, Erikson RL. Identification of an early-growth-response gene encoding a novel putative protein kinase. **Mol. Cell. Biol.** 1992 Sep;12(9):4164-9. PMCID:PMC360319

19. Freeman RM, Plutzky J, **Neel BG**. Identification of a human src homology 2-containing protein-tyrosine-phosphatase: a putative homolog of Drosophila corkscrew. **Proc. Natl. Acad. Sci. USA**. 1992 Dec 1;89(23):11239-43. PMID:PMC50525
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21. Frangioni JV, **Neel BG**. Solubilization and purification of enzymatically active glutathione S-transferase (pGEX) fusion proteins. **Anal. Biochem.**, 1993 Apr;210(1):179-87.
22. Frangioni JV, **Neel BG**. Use of a general purpose mammalian expression vector for studying intracellular protein targeting: Identification of critical residues in the nuclear lamin A/C nuclear localization signal. **J. Cell Science**, 1993 Jun;105(pt 2):481-8.
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26. Frangioni JV, Oda A, Smith M, Salzman EW, **Neel BG**. Calpain-catalyzed cleavage and subcellular relocation of protein tyrosine phosphatase 1B (PTP-1B) in human platelets. **EMBO J.** 1993 Dec;12(12):4843-56. PMID:PMC413938
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29. Frangioni JV, Moghal N, Stuart-Tilley A, **Neel BG**, Alper SL. The DNA binding domain of retinoid acid receptor beta is required for ligand-dependent suppression of proliferation. Application of general purpose of mammalian coexpression vectors. **J. Cell Science**, 1994: Apr;107(pt 4):827-38.
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33. Pei D, Lorenz U, Klingmuller U., **Neel BG**, Walsh CT. Intramolecular regulation of protein tyrosine phosphatase SH-PTP1: a new function for Src homology 2 domains. **Biochem** 1994 Dec 27;33(51):15483-93.
34. Tang TL, Freeman RM, O'Reilly AM, **Neel BG\***, Sokol SY\*. The SH2-containing protein-tyrosine phosphatase SH-PTP2 is required upstream of MAP kinase for early *Xenopus* development. **Cell** 1995 Feb 10;80(3): 473-83. PMID 7859288 **\*co-corresponding**
35. Klingmuller U, Lorenz U, Cantley LC, **Neel BG\***, Lodish HF. Specific recruitment of the SH-PTP1 to the erythropoietin receptor causes inactivation of JAK2 and termination of proliferative signals. **Cell** 1995 Mar 10;80(5):729-38. **\*co-corresponding**
36. Hausdorff SF, Bennett AM, **Neel BG\***, Birnbaum MJ. Different signaling roles of SHPTP2 in insulin-induced GLUT1 expression and GLUT4 translocation. **J. Biol. Chem.** 1995 Jun 2;270(22):12965-68. **\*co-corresponding**
37. Moghal N., **Neel BG**. Evidence for impaired retinoic acid receptor-thyroid hormone receptor AF-2 cofactor activity in human lung cancer. **Mol. Cell. Biol.** 1995 Jul;15(7):3945-59. PMCID:PMC230634
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47. Nadler MJ, Chen B, Anderson JS, Wortis HH, **Neel BG**. Protein tyrosine phosphatase SHP-1 is dispensable for FcγRIIB-mediated inhibition of B cell antigen receptor activation. **J. Biol. Chem.** 1997 Aug 8;272(32):20038-43.
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# APPENDIX C

## **Previous Four Years of Expert Testimony for Benjamin Neel, M.D., Ph.D.**

Dr. Benjamin Neel has not testified as an expert at trial or by deposition during the previous four years.